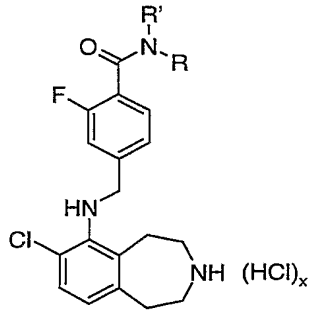
6-(4-*tert*-butylcarbamoyl-benzylamino)-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm] to obtain the title compound as a white solid (65 mg, 41%). MS (ES+) *m/z*: 386 $(M+H)^+$.

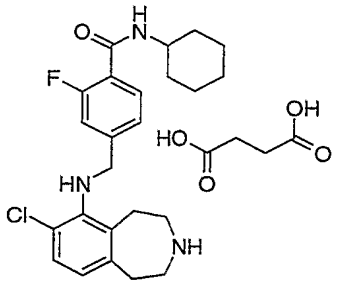
Examples 160-161 may be prepared essentially as described in Example 159 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	R'	Compound	Yield (%)	MS (ES+) *m/z*
160	*t*-Bu	Me	6-(4-*tert*-Butylcarbamoyl-3-fluoro-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride	48	404 $(M+H)^+$
161	*n*-Pr	Me	7-Chloro-6-[3-fluoro-4-(*N*-methyl-*N*-propyl-carbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	48	404 $(M+H)^+$

Example 162

7-Chloro-6-[4-(cyclohexylaminocarbonyl-)3-fluoro-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



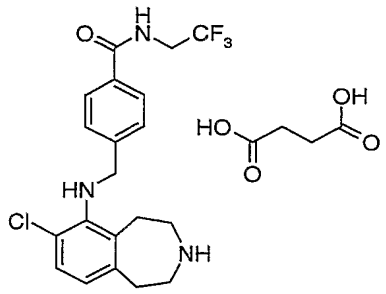
Use a method similar to the General Procedure 5-2 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol) with 4-aminomethyl-*N*-cyclohexyl-2-fluoro-benzamide (441 mg, 1.76 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-6-[4-(cyclohexylaminocarbonyl-)3-fluoro-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) followed by reverse phase semi-prep HPLC [SymmetryPrep C18, 7 □m, 19x300 mm column eluting with acetonitrile/0.1 % trifluoroacetic acid in water (1:9 to 8:2) at 20 mL/min] and SCX chromatography to give the free base of the title compound.

Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (97 mg, 15%). MS (ES+) *m/z*: 430 $(M+H)^+$.

Example 163

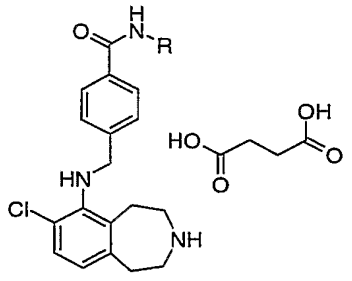
7-Chloro-6-[4-(2,2,2-trifluoroethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



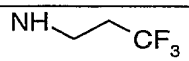
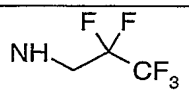
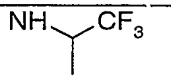
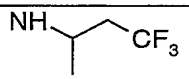
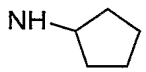
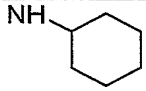
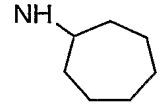
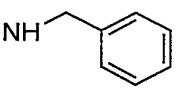
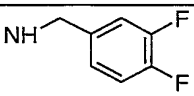
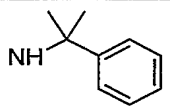
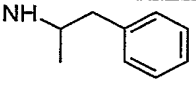
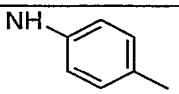
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.59 mmol) with 4-aminomethyl-*N*-(2,2,2-trifluoroethyl)-benzamide (273 mg, 1.17 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-3-(2,2,2-trifluoroacetyl)-6-[4-(2,2,2-trifluoroethyl-aminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

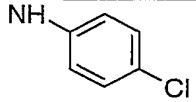
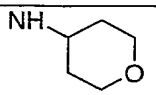
Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (191 mg, 61%). MS (ES+) *m/z*: 412 $(M+H)^+$.

Examples 164-177 may be prepared essentially as described in Example 163 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



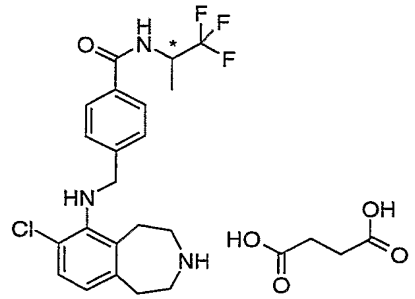
Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*

164		7-Chloro-6-[4-(3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	38	426 $(M+H)^+$
165		7-Chloro-6-[4-(2,2,3,3,3-pentafluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	41	462 $(M+H)^+$
166		(±)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	426 $(M+H)^+$
167		(±)-7-Chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	28	440 $(M+H)^+$
168		7-Chloro-6-[4-(cyclopentylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	398 $(M+H)^+$
169		7-Chloro-6-[4-(cyclohexylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	82	412 $(M+H)^+$
170		7-Chloro-6-[4-(cycloheptylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	65	426 $(M+H)^+$
171		6-[4-(Benzylaminocarbonyl)-benzylamino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	33	420 $(M+H)^+$
172		7-Chloro-6-[4-(3,4-difluoro-benzylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	456 $(M+H)^+$
173		7-Chloro-6-[4-(1-methyl-1-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	12	448 $(M+H)^+$
174		(±)-7-Chloro-6-[4-(1-methyl-2-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	36	448 $(M+H)^+$
175		7-Chloro-6-[4-(*p*-tolylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	60	420 $(M+H)^+$

176		7-Chloro-6-[4-(4-chloro-phenylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	28	440 $(M+H)^+$
177		7-Chloro-6-[4-(tetrahydro-pyran-4-yl-aminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	13	414 $(M+H)^+$

Examples 178 and 179

(-)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Dissolve (±)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (472 mg, 1.11 mmol) in DCM (50 mL) and add di-*tert*-butyl-dicarbonate (300 mg, 1.34 mmol) and a solution of sodium carbonate (2 g) in water (50 mL). Stir the reaction at room temperature for 2 h then dilute with DCM, wash with water, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) to give (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-benzo[*d*]azepine (330 mg, 57%).

Separate the two enantiomers by chiral HPLC [Chiralpak AD column, 8x30 cm, eluting with 0.2% DMEA in heptane/isopropanol (9:1)].

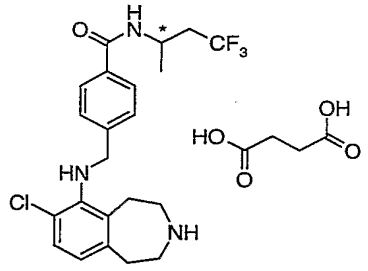
Use a method similar to the General Procedure 1-5 to deprotect the first eluting compound and purify by SCX chromatography to give (-)-7-chloro-6-[4-(2,2,2-trifluoro-

1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (-)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (50 mg, 15%). MS (ES+) *m/z*: 426 $(M+H)^+$; $[\alpha]^{20}_D$ –3.3° (c 0.5, CH_3OH).

Use a method similar to the General Procedure 1-5 to deprotect the second eluting compound and purify by SCX chromatography to give (+)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (+)-7-chloro-6-[4-(2,2,2-trifluoro-1-methyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (55 mg, 16%). MS (ES+) *m/z*: 426 $(M+H)^+$; $[\alpha]^{20}_D$ +4.4° (c 0.5, CH_3OH).

Examples 180 and 181

(+)-7-Chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (-)-7-Chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Dissolve (±)-7-chloro-3-(2,2,2-trifluoroacetyl)-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (985 mg, 2.24 mmol) in DCM (50 mL) and add di-*tert*-butyl-dicarbonate (605 mg, 3.36 mmol) and a solution of sodium carbonate (2 g) in water (50 mL). Stir the mixture at room temperature for 1 h then dilute with DCM, wash with water, dry over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1,

5:1 and 3:1) to give (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-benzo[*d*]azepine.

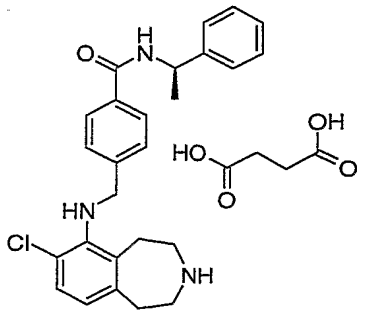
Separate the two enantiomers by chiral HPLC [Chiralpak AD column, 8x30 cm, eluting with heptane/isopropanol/0.2% DMEA in methanol (90:5:5)].

Use a method similar to the General Procedure 1-5 to deprotect the first eluting compound and purify by SCX chromatography to give (+)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (+)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (186 mg, 15%). MS (ES+) *m/z*: 440 $(M+H)^+$; $[\alpha]^{20}_D$ +6.5° (c 0.5, CH_3OH).

Use a method similar to the General Procedure 1-5 to deprotect the second eluting compound and purify by SCX chromatography to give (-)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 2-1 to give (-)-7-chloro-6-[4-(1-methyl-3,3,3-trifluoro-propylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate as a white solid (191 mg, 15%). MS (ES+) *m/z*: 440 $(M+H)^+$; $[\alpha]^{20}_D$ –5.2° (c 0.5, CH_3OH).

Example 182

(*R*)-(+)-7-Chloro-6-[4-(1-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

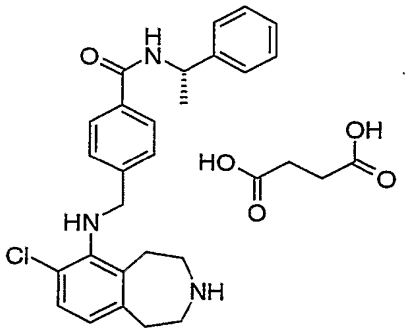


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.59 mmol) with (*R*)-4-aminomethyl-*N*-(1-phenyl-ethyl)-benzamide (298 mg, 1.17 mmol) in toluene (15 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give (*R*)-(+)-7-chloro-6-[4-(1-phenyl-ethylcaminocarbonyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)- 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (158 mg, 49%). MS (ES+) *m/z*: 434 $(M+H)^+$; $[\alpha]^{20}_D$ +18.7° (c 0.5, CH_3OH).

Example 183

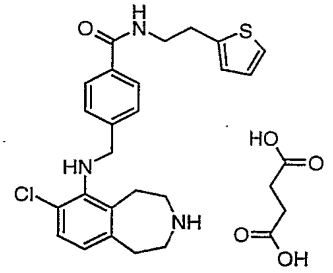
(*S*)-(-)-7-Chloro-6-[4-(1-phenyl-ethylaminocarbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 182, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.59 mmol) and (*S*)-4-aminomethyl-*N*-(1-phenyl-ethyl)-benzamide (298 mg, 1.17 mmol) to give the title compound as a white solid (95 mg, 29%). MS (ES+) *m/z*: 434 $(M+H)^+$; $[\alpha]^{20}_D$ -20.1° (c 0.5, CH_3OH).

Example 184

7-Chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

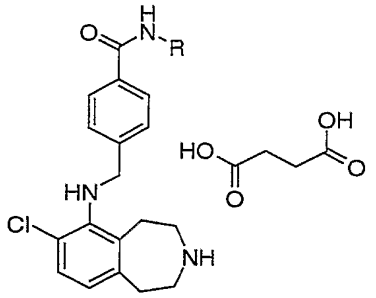


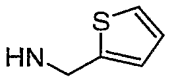
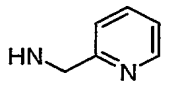
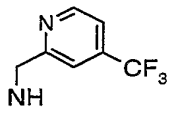
Use a method similar to the General Procedure 5-3, react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.588 mmol) with 4-aminomethyl-*N*-(2-thiophen-2-yl-ethyl)-benzamide (306 mg, 1.176 mmol) using palladium(II) acetate (26 mg, 0.118 mmol), tris(dibenzylideneacetone)dipalladium(0) (53 mg, 0.059 mmol), BINAP (220 mg, 0.353 mmol) and cesium carbonate (383 mg, 1.176 mmol) in dioxane (6 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 7:3 and 1:1) to give 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (233 mg, 91%). MS (ES+) *m/z*: 535 $(M+H)^+$.

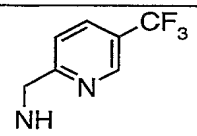
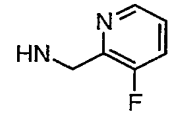
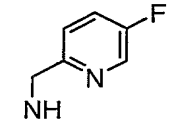
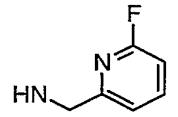
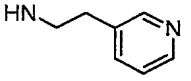
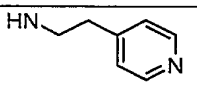
Use a method similar to the General Procedure 1-2, using 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (223 mg, 0.416 mmol), to give 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (145 mg, 79%) that was used without any further purification.

Use a method similar to the General Procedure 2-1, using 7-chloro-6-{4-[(2-thiophen-2-yl-ethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (145 mg, 0.330 mmol), to give the title compound as a solid (123 mg, 67%). MS (ES+) *m/z*: 440 $(M+H)^+$.

Examples 185-194 may be prepared essentially as described in Example 184 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.

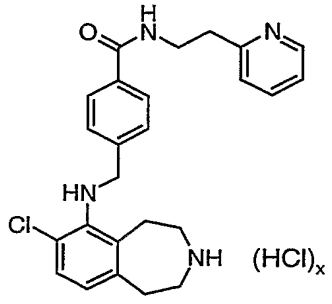


Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
185		7-Chloro-6-{4-[(thiophen-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	426 $(M+H)^+$
186		7-Chloro-6-{4-[(pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	49	421 $(M+H)^+$
187		7-Chloro-6-{4-[(3-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	39	489 $(M+H)^+$
188		7-Chloro-6-{4-[(4-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	26	489 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
189		7-Chloro-6-{4-[(5-trifluoromethyl-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	29	489 $(M+H)^+$
190		7-Chloro-6-{4-[(3-fluoro-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	37	439 $(M+H)^+$
191		7-Chloro-6-{4-[(5-fluoro-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	51	439 $(M+H)^+$
192		7-Chloro-6-{4-[(6-fluoro-pyridin-2-ylmethyl)-carbamoyl]-benzylamino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	439 $(M+H)^+$
193		7-Chloro-6-[4-(2-pyridin-3-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	435 $(M+H)^+$
194		7-Chloro-6-[4-(2-pyridin-4-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	27	435 $(M+H)^+$

Example 195

7-Chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-3 to react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

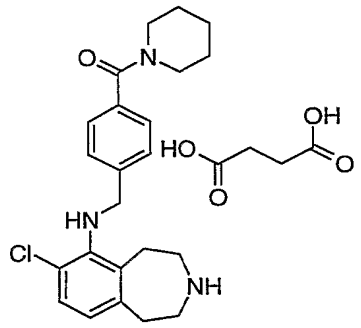
(200 mg, 0.471 mmol) and 4-aminomethyl-*N*-(2-pyridin-2-yl-ethyl)-benzamide (241 mg, 0.942 mmol) using palladium(II) acetate (21 mg, 0.094 mmol), tris(dibenzylideneacetone)dipalladium(0) (43 mg, 0.047 mmol), BINAP (176 mg, 0.283 mmol) and cesium carbonate (307 mg, 0.942 mmol) in dioxane (5 mL). Purify by chromatography on silica gel eluting with hexane and hexane/EtOAc/DCM/methanol (7:1:1:1) to give 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (107 mg, 43%). MS (ES+) *m/z*: 531 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (107 mg, 0.202 mmol), to give 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (85 mg, 97%) that was used without any further purification.

Use a method similar to the General Procedure 2-2, using 7-chloro-6-[4-(2-pyridin-2-yl-ethylcarbamoyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (85 mg, 0.195 mmol), to give the title compound as a solid (103 mg, 97 %). MS (ES+) *m/z*: 435 $(M+H)^+$.

Example 196

7-Chloro-6-[4-(piperidine-1-carbonyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



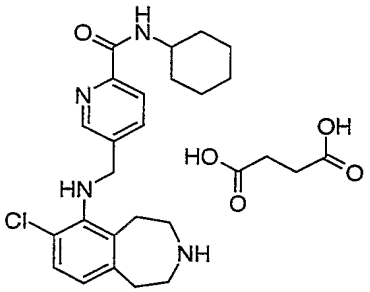
Using a method similar to the General Procedure 5-2, react 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

(500 mg, 1.17 mmol) with 4-(piperidin-1-ylcarbonyl)-benzylamine (308 mg, 1.41 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-6-[4-(piperidine-1-carbonyl)-benzylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (284 mg, 47%). MS (ES+) *m/z*: 398 $(M+H)^+$.

Example 197

7-Chloro-6-[2-(cyclohexylaminocarbonyl-pyridin-5-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



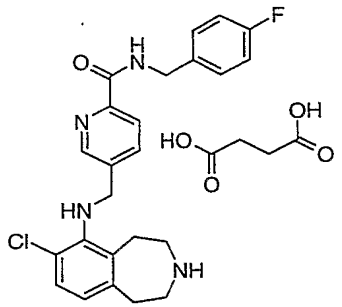
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (348 mg, 0.82 mmol) with 5-aminomethyl-pyridine-2-carboxylic acid cyclohexylamide (200 mg, 0.86 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1, 7:1 and 5:1) to give 7-chloro-6-[2-(cyclohexylaminocarbonyl-pyridin-5-ylmethyl)-amino]-3-(2,2,2-trifluoroacetyl)- 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as oil.

Use a method similar to the General Procedure 1-3 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (1:0, 20:1. 10:1 and 7:1) to give the free base of the title compound.

Use a method similar to the General Procedure 2-1 to give the title compound as a yellow solid (147 mg, 34%). MS (ES+) *m/z*: 413 $(M+H)^+$.

Example 198

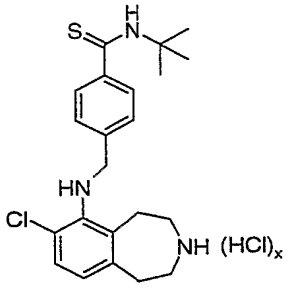
7-Chloro-6-[2-(4-fluoro-benzylaminocarbonyl)-pyridin-5-ylmethyl]-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 197, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-aminomethyl-pyridine-2-carboxylic acid 4-fluoro-benzylamide (28% yield, MS (ES+) m/z 439).

Example 199

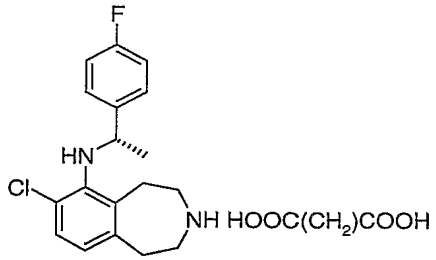
7-Chloro-6-(4-*tert*-butylthiocarbamoyl-benzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Combine 6-(4-*tert*-butylcarbamoyl-benzylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo-[*d*]azepine (0.3 g, 0.67 mmol), 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4- diphosphetane-2,4-disulfide (Lawesson's reagent) (0.3, g, 0.67 mmol) and anhydrous 1,4-dioxane (10 mL) in a sealed tube and heat at 100°C for 5 h. Cool the reaction mixture to ambient temperature, evaporate the solvent and purify the residue by SCX

Example 200

(*S*)-(-)-7-Chloro-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

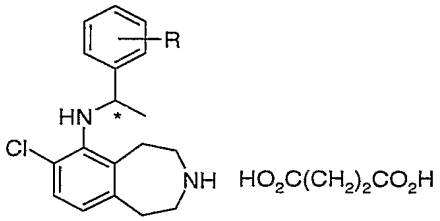


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (7.0g, 16.4mmol) with (*S*)-1-(4-fluorophenyl)ethylamine (6.9 g, 49.3 mmol) in toluene (175 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to give 7-chloro-6-[1-(*S*)-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.96 g, 58%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-[1-(*S*)-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.92 g, 9.5 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 80:20) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from ethanol and methyl-*t*-butyl ether. Filter and dry the solid in a vacuum oven at 60°C overnight to obtain the title compound (3.4 g, 83 %). MS (ES+) *m/z*: 319 $(M+H)^+$; $[\alpha]^{20}_D$ –102.8° (c 0.5, MeOH).

Examples 201-209 may be prepared essentially as described in Example 200 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1

(General Procedure 5-2), optical rotation and MS (ES+) data are shown in the Table below.

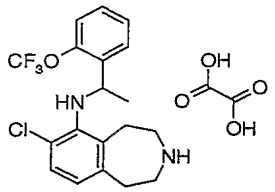


Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS
201	4-F	(*R*)-(+)-7-Chloro-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	69	+89.2° (c 0.5, MeOH)	319 $(M+H)^+$
202	2-F	(+)-7-Chloro-6-[1-(2-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	62	+105° (c 0.5, MeOH)	319 $(M+H)^+$
203	4-CN	(+)-7-Chloro-6-[1-(4-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	60	+142.1° (c 0.5, MeOH)	326 $(M+H)^+$
204	4-CN	(-)-7-Chloro-6-[1-(4-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	52	-149.3° (c 0.5, MeOH)	326 $(M+H)^+$
205	2,3-diF	(+)-7-Chloro-6-[1-(2,3-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	14	+99.3° (c 0.5, MeOH)	337 $(M+H)^+$
206	2,3-diF	(-)-7-Chloro-6-[1-(2,3-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	80	-107.9° (c 0.5, MeOH)	337 $(M+H)^+$
207	2,4-diF	(+)-7-Chloro-6-[1-(2,4-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	94	+101.4° (c 0.5, MeOH)	337 $(M+H)^+$
208	2,4-diF	(-)-7-Chloro-6-[1-(2,4-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	96	-107.9° (c 0.5, MeOH)	337 $(M+H)^+$

Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS
209	3,5-diCF_3	(-)-7-Chloro-6-[1-(3,5-bis-trifluoromethyl-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	99	-93° (c 0.5, MeOH)	437 $(M+H)^+$

Example 210

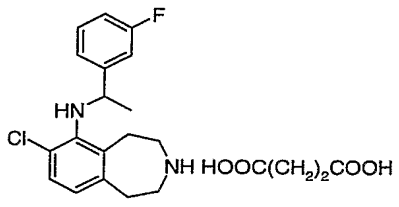
(+)-7-Chloro-6-[(2-trifluoromethoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) with 1-(2-trifluoromethoxyphenyl)-ethylamine Isomer 2 at 90°C for 15 h. Use a method similar to the General Procedure 1-2 and purify by reverse phase preparative HPLC to give the free base of the title compound. Use a method similar to the General Procedure 2-5 to give the title compound (27 mg, 16 %). HPLC t_R = 4.2 min (Chiralpak AD 4.6x150 mm, 3 micron column, 1.0 mL/min of 94.8/5/0.2 heptane/ethanol/dimethyethylamine isocratic; detector is at 225 nm); HRMS calcd for $C_{19}H_{20}ClF_3N_2O$ 385.1294, found 385.1285; $[\alpha]^{20}_D$ +95.4° (c 0.5, MeOH).

Example 211

(±)-7-Chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

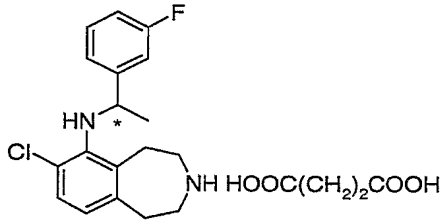


Add palladium(II) acetate (27 mg, 0.12 mmol), BINAP (146 mg, 0.24 mmol), cesium carbonate (270 mg, 0.8 mmol) and (±)-1-(3-fluorophenyl)-ethylamine (230 mg, 1.6 mmol) to a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.6 mmol) in toluene (9 mL). Degas the slurry and fill with nitrogen. Heat the mixture to 95°C for 16 h. Add additional palladium(II) acetate (0.1 equiv.) and BINAP (0.2 equiv.) and continue heating the reaction for an additional 24 h. Cool the mixture, dilute with EtOAc (50 mL) then filter through Celite®. Concentrate the filtrate and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography to obtain (±)-7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (138 mg, 56%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (132 mg, 0.3 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (98 mg, 70 %). MS (ES+) *m/z*: 319 $(M+H)^+$.

Example 212

(+)-7-Chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

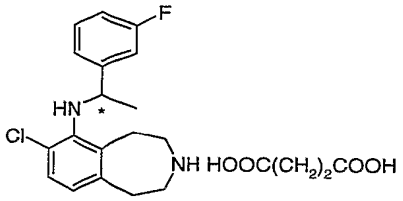


Separate the two enantiomers of (±)-7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate by normal phase chromatography (Chiralpak AD 2x25 cm, elute with 95:5 heptane/isopropanol with 0.2 % DMEA).

Use a method similar to the General Procedure 2-1 to obtain the title compound [23 mg, 30% recovery, 99% ee (Chiralpak AD, 4.6x250 mm, eluent: 95:5 heptane/isopropanol, with 0.2% DMEA, 1.0 mL/min)]. MS (ES+) *m/z*: 319 $(M+H)^+$; $[\alpha]^{20}_D$ +64° (c 0.5, MeOH).

Example 213

(-)-7-Chloro-6-[1-(3-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



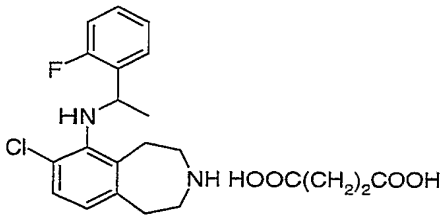
Add tris(dibenzylideneacetone)dipalladium(0) (3.4 g, 3.8 mmol), BINAP (4.7 g, 7.5 mmol), cesium carbonate (8.6 g, 26.3 mmol) and 1-(3-fluorophenyl)-ethylamine Isomer 2 (5.8 g, 41.3 mmol) to a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (8.0 g, 18.8 mmol) in toluene(225 mL). Degas the slurry and fill with nitrogen. Heat the mixture to 95 °C for 8 h. Add additional tris(dibenzylideneacetone)dipalladium(0) (0.1 equiv.), and BINAP (0.2 equiv.). Continue heating the reaction for an additional 16 h. Cool the mixture, dilute with EtOAc (200 mL) then filter thru Celite®. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) followed by SCX chromatography to obtain 7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (6.0 g, 78%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-[1-(3-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (6.0 g, 14.4 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from ethanol and methyl-*t*-butyl ether. Filter and dry the solid under vacuum at 60°C

overnight to obtain the title compound [5.3 g, 84 % yield, 99% ee (Chiralpak AD, 4.6x250 mm, eluent: 95:5 heptane/EtOH, with 0.2% DMEA, 1.0 mL/min)]. MS (ES+) *m/z*: 319 $(M+H)^+$; $[\alpha]^{20}_D$ –90.6° (c 0.5, MeOH).

Example 214

(±)-7-Chloro-6-[1-(2-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

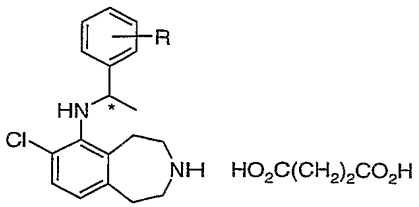


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.6 mmol) with (±)-1-(2-fluorophenyl)-ethylamine (206 mg, 1.5 mmol) in toluene (5 mL). Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain (±)-7-chloro-6-[1-(2-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (86 mg, 35%). GC-MS *m/z*: 414 (M^+).

Use a method similar to the General Procedure 1-3 to deprotect (±)-7-chloro-6-[1-(2-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (85 mg, 0.2 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (70 mg, 80 %). MS (ES+) *m/z*: 319 $(M+H)^+$.

Examples 215-216 may be prepared essentially as described in Example 214 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1

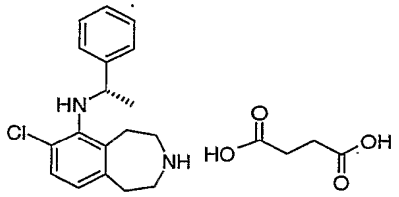
(General Procedure 5-1), optical rotation and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS (ES+) *m/z*
215	3-CN	(+)-7-Chloro-6-[1-(3-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	58	+100.7° (c 0.5, MeOH)	326 $(M+H)^+$
216	3-CN	(-)-7-Chloro-6-[1-(3-cyanophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	90	-109.7° (c 0.5, MeOH)	326 $(M+H)^+$

Example 217

(*S*)-(-)-7-Chloro-6-(1-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

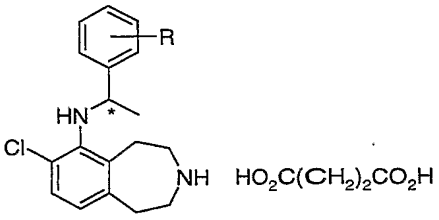


Add palladium(II) acetate (396 mg, 1.8 mmol), BINAP (2.2 g, 3.5 mmol), cesium carbonate (8.0 g, 24.6 mmol), and 1*S*-(-)-methylbenzylamine (6.4 g, 52.9 mmol) to a solution of 7-chloro-6-trifluoromethanesulfonyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (7.5 g, 17.6 mmol) in toluene(173 ml). Degas the slurry and fill with nitrogen. Heat the mixture to 95°C for 16 h. GC/MS shows some starting material still present after 16 h, so add additional palladium(II) acetate (0.1 equiv.), BINAP, and 1*S*-(-)-methylbenzylamine (1.0 equiv..). Continue heating the reaction for an additional 24 h. Cool the mixture, dilute with EtOAc (250 ml) then filter through Celite®. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc/methanol (84:15:1) followed by SCX chromatography to give (*S*)-7-

chloro-6-(1-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (4.38 g, 63%). GC-MS *m/z*: 396 (M^+).

Use a method similar to the General Procedure 1-1 to deprotect (*S*)-7-chloro-6-(1-phenyl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine (4.3 g, 10.8 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99/1 to 80/20) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from ethanol and methyl-*t*-butyl ether. Filter and dry the solid in a vacuum oven at 70°C overnight to obtain the title compound (3.6 g, 80%). MS (ES+) *m/z*: 301 $(M+H)^+$. $[\alpha]^{20}_D$ –95.6° (c 0.5, MeOH).

Examples 218-227 may be prepared essentially as described in Example 217 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1, optical rotation or enantiomeric excess (determined by chiral HPLC) and MS (ES+) data are shown in the Table below.



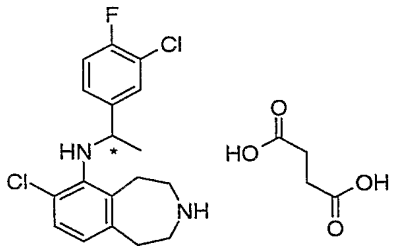
Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent) or ee (%)	MS (ES+) *m/z*
218	H	(*R*)-(+)-7-Chloro-6-(1-phenyl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	47	+100.5° (c 0.5, MeOH)	301 $(M+H)^+$
219	4-CF_3	(+)-7-Chloro-6-[1-(4-trifluoromethyl-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	+95.7° (c 0.5, MeOH)	369 $(M+H)^+$

Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent) or ee (%)	MS (ES+) *m/z*
220	3-CF_3	7-Chloro-6-[1-(3-trifluoromethyl-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, Isomer 1	90	95% ee	369 $(M+H)^+$
221	3,4-diF	7-Chloro-6-[1-(3,4-trifluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 1	28	94 % ee	337 $(M+H)^+$
222	3,4-diF	(+)-7-Chloro-6-[1-(3,4-trifluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate	81	+89.0° (c 0.5, MeOH)	337 $(M+H)^+$
223	3,4,5-triF	7-Chloro-6-[1-(3,4,5-trifluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 2	40	ND	355 $(M+H)^+$
224	3-OCH_3	7-Chloro-6-[1-(3-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride, Isomer 1	53	ND	331 $(M+H)^+$
225	4-OCH_3	7-Chloro-6-[1-(4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride, Isomer 1	53	>99 % ee	331 $(M+H)^+$
226	4-OPh	7-Chloro-6-[1-(4-phenoxyphenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 1	27	ND	393 $(M+H)^+$
227	4-OPh	7-Chloro-6-[1-(4-phenoxyphenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine Succinate, Isomer 2	27	ND	393 $(M+H)^+$

ND = Not determined

Example 228

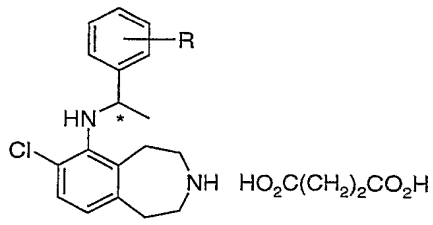
(-)-7-Chloro-6-[1-(3-chloro-4-fluoro-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) with 1-(3-chloro-4-fluoro-phenyl)-ethylamine Isomer 1 (226 mg, 1.3 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:7) to give 7-chloro-6-[1-(3-chloro-4-fluoro-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (293 mg, 65%).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(3-chloro-4-fluoro-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (293 mg, 0.65 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to give the free base of the title compound as an oil (157 mg, 68%). MS (ES+) *m/z*: 353 $(M+H)^+$. Use a method similar to preparation E-1 to convert the free base to the title compound. $[\alpha]^{20}_D$ –115.9° (c 0.5, MeOH).

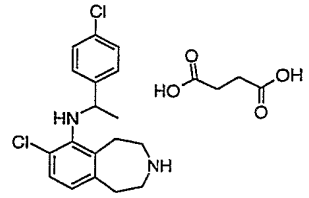
Examples 229-235 may be prepared essentially as described in Example 228 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3), optical rotation and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	$[\alpha]^{20}_D$ (c, solvent)	MS
229	3-Cl	(+)-7-Chloro-6-[1-(3-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	17	+119.6° (c 0.5, CH_3OH)	335 $(M+H)^+$
230	2-Cl	(+)-7-Chloro-6-[1-(2-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	30	+45.0° (c 0.5, CH_3OH)	335 $(M+H)^+$
231	4-CH_3	(*R*)-(+)-7-Chloro-6-(1-*p*-tolylethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	57	+107° (c 0.5, MeOH)	315 $(M+H)^+$
232	4-CH_3	(*S*)-(-)-7-Chloro-6-(1-*p*-tolylethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	-97.2° (c 0.5, MeOH)	315 $(M+H)^+$
233	3-Cl,4-F	(+)-7-Chloro-6-[1-(3-chloro-4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	+115.0° (c 0.5, CH_3OH)	353 $(M+H)^+$
234	3,5-diF	(-)-7-Chloro-6-[1-(3,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	50	-97.6° (c 0.5, MeOH)	337 $(M+H)^+$
235	3,5-diF	(+)-7-Chloro-6-[1-(3,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	41	+91.0° (c 0.5, MeOH)	337 $(M+H)^+$

Example 236

(±)-7-Chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

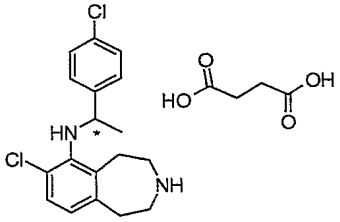


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (852 mg, 2.0 mmol) and (±)-4-chloro-(α-methyl)benzylamine (622 mg, 4.0 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain (±)-7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (326 mg, 38%). MS (ES+) *m/z*: 431 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (±)-7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (61 mg, 100%). MS (ES+) *m/z*: 335 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 237 and 238

(-)-7-Chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



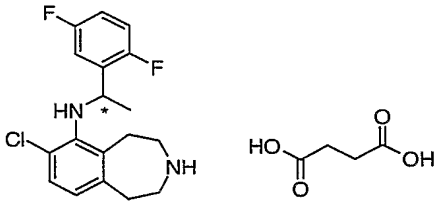
Submit (±)-7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (326 mg, 0.76 mmol) to chiral chromatography (Chiralpak AD, 4.6x150 mm, eluting with heptane/ethanol (9:1) with 0.2% DMEA, 1mL/min) to provide the two enantiomers: 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (102 mg, t_R = 5.25 min) and 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (110 mg, t_R = 6.40 min).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (Example 237, 82 mg, 100%). MS (ES+) *m/z*: 335 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound. $[\alpha]^{20}_D$ –127.7° (c 0.5, CH_3OH).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give 7-chloro-6-[1-(4-chlorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (Example 238, 68 mg, 78%). MS (ES+) *m/z*: 335 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound. $[\alpha]^{20}_D$ +133.6° (c 0.5, CH_3OH).

Examples 239 and 240

7-Chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 1, and 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate Isomer 2



Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (550 mg, 1.27 mmol) and crude (±)-α-methyl-(2',5'-difluoro)benzylamine (400 mg).

Separate the two enantiomers by chiral chromatography (eluent: 75:20:5 heptane/isopropanol/methanol, 4.6x250 mm Chiralpak AD, 1 mL/min, uv 260 nm) to obtain 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-

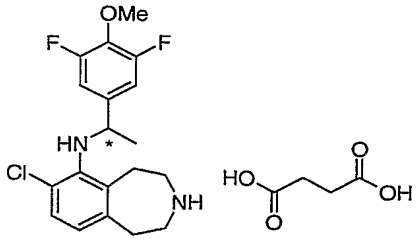
tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 [150 mg, 29%; chiral HPLC: t_R = 4.5 min; MS (ES+) *m/z*: 433 $(M+H)^+$] and 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 [130 mg, 25%; chiral HPLC: t_R = 5.5 min; MS (ES+) *m/z*: 433 $(M+H)^+$], both as opaque oils which solidify upon standing to off-white waxy solids.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (140 mg, 0.32 mmol). Purify by SCX chromatography to give 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (102 mg, 95%) as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the Isomer 1 of the title compound (130 mg, 95%) as an off-white solid. MS (ES+) *m/z*: 337 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (125 mg, 0.29 mmol). Purify by SCX chromatography to give 7-chloro-6-[1-(2,5-difluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (87.7 mg, 90%) as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the Isomer 2 of the title compound (117 mg, 99%) as an off-white solid. MS (ES+) *m/z*: 337 $(M+H)^+$.

Example 241

(-)-7-Chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

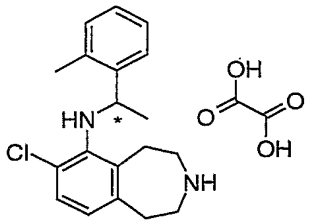


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine

(300 mg, 0.7 mmol) and crude α-methyl-(3',5'-difluoro-4'-methoxy)benzylamine (380 mg). Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) followed by chiral chromatography [heptane/isopropanol/dimethylethylamine (90:10:0.2), 4.6x250 mm Chiralpak AD, 1 mL/min, uv 250 nm] to give 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 [59 mg, 18% yield, 99% ee, chiral HPLC: t_R = 6.0 min; MS (ES-) *m/z*: 461 $(M-H)^-$] and 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 [50 mg, 15% yield, 99% ee, chiral HPLC: t_R = 7.7 min; MS (ES-) *m/z*: 461 $(M-H)^-$]. Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (50 mg, 0.14 mmol). Purify by SCX chromatography to give 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (35 mg, 70%) as a yellow oil. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[1-(3,5-difluoro-4-methoxy-phenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (35 mg, 0.10 mmol), to give the title compound (44 mg, 97%) as an off-white powder. MS (ES+) *m/z*: 367 $(M+H)^+$; $[\alpha]^{20}_D$ –107.0° (c 0.5, CH_3OH).

Example 242

(+)-7-Chloro-6-[(2-methylphenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

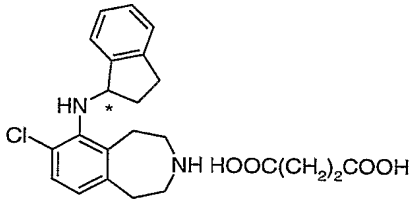


Usa a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) with (*R*)-1-(2-methyl)-ethylamine (162 mg, 1.2 mmol) at 90°C for 17 h. Deprotect according to the General Procedure 1-2. Purify by reverse phase preparative HPLC and form the oxalate salt according to the General Procedure 2-5 to give the title compound (72 mg, 51 %). HPLC t_R = 4.0 min (Chiralpak AD 4.6x150 mm, 3 micron

column, 1.0 mL/min of 89.8:10:0.2 heptane/isopropanol/DMEA, isocratic; detector is at 225 nm); HRMS calcd for $C_{19}H_{23}ClN_2$ 315.1628, found 315.1623. $[\alpha]^{20}_D$ +67.2° (c 0.5, CH_3OH).

Example 243

(+)-7-Chloro-6-(indan-1-ylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

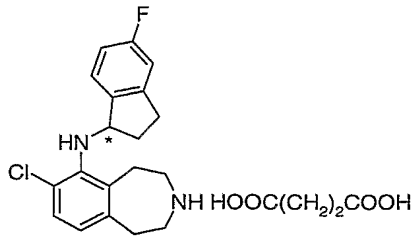


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.5 mmol) with (*R*)-1-aminoindan (188 mg, 1.4 mmol) in toluene (5 mL). Purify by chromatography on silica gel eluting with hexane / EtOAc (9:1 to 1:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to give 7-chloro-6-(indan-1-ylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (129 mg, 67%). GC-MS *m/z*: 408 (M^+).

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-(indan-1-ylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (125 mg, 0.3 mmol) and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 80:20) to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (104 mg, 78 %). MS (ES+) *m/z*: 313 $(M+H)^+$. $[\alpha]^{20}_D$ +73.9° (c 0.5, MeOH).

Example 244

(+)-7-Chloro-6-(5-fluoro-indan-1-ylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

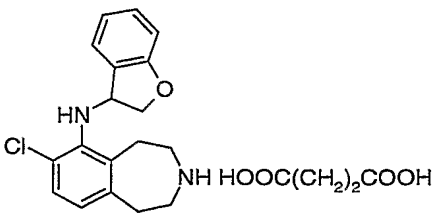


Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (210 mg, 0.5 mmol) with 5-fluoro-indan-ylamine Isomer 1 (161 mg, 1.1 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography to obtain 7-chloro-6-[1-(3,5-bis-trifluoromethyl-phenyl)-ethylamino]- 3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine Isomer 1 (616 mg, 99%).

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(5-fluoro-indan-ylamine)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine Isomer 1 (200 mg, 0.5 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99/1 to 90/10) to give the free base of the title compound. Use Preparation E-1 to give the title compound (140 mg, 66 %). MS (ES+) *m/z*: 331 $(M+H)^+$. $[\alpha]^{20}_D$ + 80.0° (C, 0.5, MeOH)

Example 245

(±)-7-Chloro-6-(2,3-dihydro-benzofuran-3-ylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



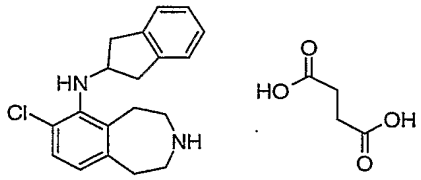
Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) with 2,3-dihydro-benzofuran-3-ylamine (prepared as described in WO 0069816) (0.14 g, 1.1 mmol) at 90°C for 18 h.

Use a method similar to the General Procedure 1-2 and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 4.6x150 mm, 5 micron column, 1 mL/min of 0.1% TFA in water/ACN (9:1 to 1:9) over 30 min, detector at 230 and 254 nm].

Use a method similar to the General Procedure 2-1 to give the title compound (4.3 mg, 3%). HRMS calcd for $C_{18}H_{19}ClN_2O$ 315.1264, found 315.1256.

Example 246

7-Chloro-6-(indan-2-yl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

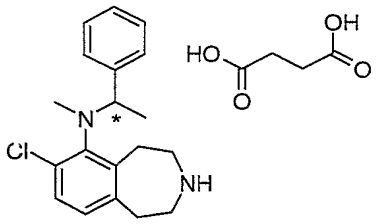


Use a method similar to the General Procedure 5-3, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) and 2-aminoindane (400 mg, 3.0 mmol), to give 7-chloro-6-(indan-2-yl-amino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a slightly yellow oil (354 mg, 86%). MS (ES+) *m/z*: 409 $(M+H)^+$.

Using a method similar to the General Procedure 1-1, deprotect 7-chloro-6-(indan-2-yl-amino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (354 mg, 0.87 mmol) to obtain 7-chloro-6-(indan-2-yl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a pale-yellow oil (166 mg, 61%). MS (ES+) *m/z*: 313 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 247

(-)-7-Chloro-6-[(*N*-methyl)-1-phenylethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

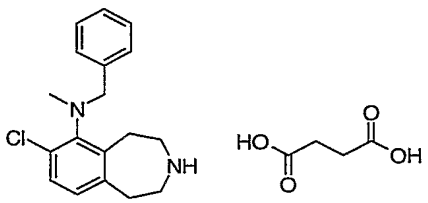


Dissolve (-)-7-chloro-6-(1-phenyl-ethylamine)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (192 mg) in DCE (5 mL) and add acetic acid (0.33 mL, 5.8 mmol), formaldehyde (37% solution; 0.5 mL) and sodium triacetoxyborohydride (570 mg, 2.7 mol) and stir the reaction at ambient temperature for 16 h. Dilute the reaction with DCM and wash with 1N aqueous NaOH. Dry the organic layers over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (20:1, 10:1 and 5:1) to give (-)-7-chloro-6-(methyl-1-phenylethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 to deprotect (-)-7-chloro-6-(methyl-1-phenylethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (176 mg, 85%). MS (ES+) *m/z*: 315 $(M+H)^+$. $[\alpha]^{20}_D$ –5.4° (c 0.5, CH_3OH).

Example 248

7-Chloro-6-[(*N*-methyl)-benzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

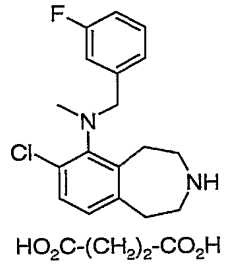


Dissolve 6-benzylamino-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (330 mg, 0.86 mmol) in DCM (3 mL) and add triethylamine (250 □L, 1.8 mmol) followed by di-*tert*-butyl-dicarbonate (260 mg, 1.2 mmol). Stir at ambient temperature for 1 h. Pour the mixture into water (250 mL), extract with DCM (3x25 mL) and concentrate *in vacuo* to give, after chromatography on silica gel eluting with hexane/EtOAc (9:1), 6-benzylamino-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (260 mg, 78%).

Dissolve 6-benzylamino-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (50 mg, 0.11 mmol) in acetonitrile (3 mL) and add a solution of formaldehyde in water (37%, 85 μL, 0.97 mmol) followed by sodium cyanoborohydride (16.5 mg, 0.26 mmol). Heat the solution to reflux 1 h, cool to ambient temperature, add glacial acetic acid (0.25 mL) and stir 72 h. Pour the mixture into water (100 mL) containing methanol (1 mL), extract with DCM (3x20 mL), wash the organic extracts with brine, dry over $MgSO_4$, filter and concentrate *in vacuo*. Dissolve the resulting residue in DCM (5 mL), and add trifluoroacetic acid (2 mL). Stir for 2 h at ambient temperature and evaporate the solvent. Purify by SCX chromatography. Use a method similar to the General Procedure 2-1 to give the title compound (45 mg, 95%). MS (ES+) *m/z*: 301 $(M+H)^+$.

Example 249

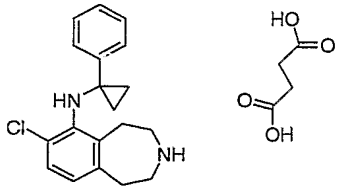
7-Chloro-6-[(*N*-methyl)-3-fluorobenzylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



The title compound may be prepared essentially as described in Example 248 by using 7-chloro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (85% yield and MS (ES+) *m/z* 319 $(M+H)^+$).

Example 250

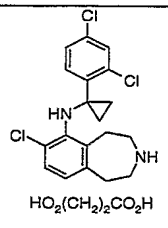
7-Chloro-6-(1-phenyl-cyclopropylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-2 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.47 mmol) with 1-phenyl-cyclopropylamine (0.2 g, 1.41 mmol) using tris(dibenzylideneacetone)dipalladium(0) (43.0 mg, 0.05 mmol), BINAP (0.1 g, 0.15 mmol) and cesium carbonate (0.3 g, 0.97 mmol) at 90°C for 17 h to obtain 7-chloro-6-(1-phenyl-cyclopropylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

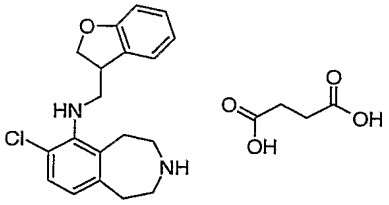
Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (85 mg, 33%).

Example 251 may be prepared essentially as described in Example 250 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-(2,4-dichlorophenyl)-cyclopropylamine. The overall yield (3 steps) is shown in the Table below.

Ex.	Structure	Compound	Yield (%)
251		7-Chloro-6-[1-(2,4-dichlorophenyl)-cyclopropylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	19

Example 252

(±)-7-Chloro-6-(2,3-dihydro-benzofuran-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

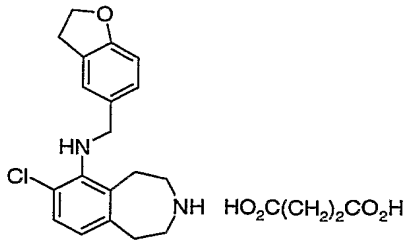


Use a method similar to the General Procedure 5-2 to couple 2,3-dihydro-benzofuran-3-yl-methylamine (prepared as described in WO 0069816) (0.14 g, 1.1 mmol) with 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) at 90°C for 18 h.

Use a method similar to the General Procedure 1-2 to deprotect 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 4.6x150 mm 5 micron column, 1 mL/min of 1% TFA in water/ACN (9:1 to 1:9) over 30 min, detector at 230 and 254 nm]. Use a method similar to the General Procedure 2-1 to give the title compound (4.3 mg, 3%).

Example 253

7-Chloro-6-[(2,3-dihydrobenzo[b]furan-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



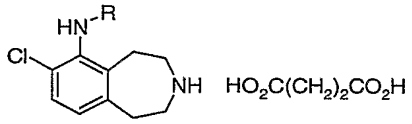
Suspend commercially available 2,3-dihydrobenzo[*b*]furan-5-yl-methylamine hydrochloride (1.0 g, 5.4 mmol) in DCM (100 mL). Add 1N aqueous NaOH (15 mL) and stir until all solids dissolve. Add two spatulas of NaCl. Stir the mixture and extract twice with DCM. Combine the organic layers, dry over Na_2SO_4, and concentrate in *vacuo* to

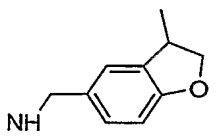
obtain 2,3-dihydrobenzo[*b*]furan-5-yl-methylamine (650 mg, 81%). MS (ES+) *m/z*: 133 $(M+H-NH_3)^+$.

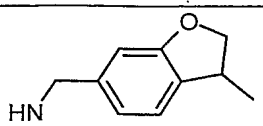
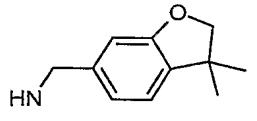
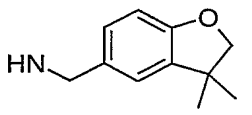
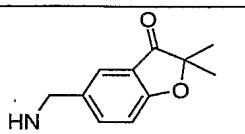
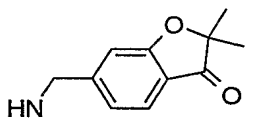
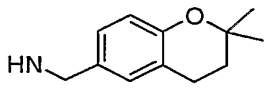
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (426 mg, 1.0 mmol) with 5-aminomethyl-2,3-dihydrobenzo[*b*]furane (223 mg, 1.5 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain 7-chloro-6-[(2,3-dihydrobenzo[b]furan-5-yl)-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (244 mg, 58%). MS (ES+) *m/z*: 425 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[(2,3-dihydrobenzo[b]furan-5-yl)-methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to give the free base of the title compound (105 mg, 32%). MS (ES+) *m/z*: 329 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Examples 254-260 may be prepared essentially as described in Example 253 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.

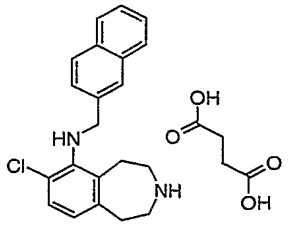


Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
254		(±)-7-Chloro-6-[*C*-(3-methyl-2,3-dihydro-benzofuran-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	50	343 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
255		(±)-7-Chloro-6-[*C*-(3-methyl-2,3-dihydro-benzofuran-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	66	343 $(M+H)^+$
256		7-Chloro-6-[*C*-(3,3-dimethyl-2,3-dihydro-benzofuran-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	57	357 $(M+H)^+$
257		7-Chloro-6-[*C*-(3,3-dimethyl-2,3-dihydro-benzofuran-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	64	357 $(M+H)^+$
258		7-Chloro-6-[*C*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-5-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	47	371 $(M+H)^+$
259		7-Chloro-6-[*C*-(2,2-dimethyl-3-oxo-2,3-dihydro-benzofuran-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	67	371 $(M+H)^+$
260		7-Chloro-6-[(2,2-dimethyl-chroman-6-yl)-methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	24	371 $(M+H)^+$

Example 261

7-Chloro-6-(naphthalen-2-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

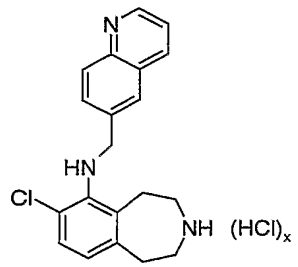


Use a method similar to the General Procedure 5-2 to couple 2-aminomethylnaphthalene (prepared as described in WO 9509159) (0.17 g, 1.1 mmol) with 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.15 g, 0.35 mmol) at 90°C for 18 h.

Use a method similar to the General Procedure 1-2 to give the free base of the title compound. HRMS calcd for $C_{21}H_{21}ClN_2$ 337.1471, found 337.1461. Use a method similar to the General Procedure 2-1 to give the title compound (104 mg, 66 % overall).

Example 262

7-Chloro-6-[(quinolin-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

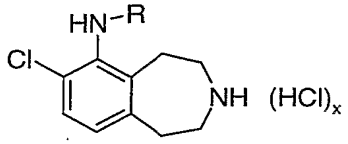


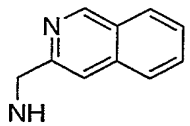
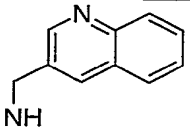
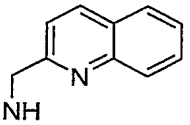
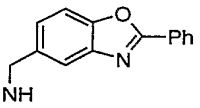
Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 6-aminomethyl-quinoline (0.2 g, 1.06 mmol) with tris(dibenzylideneacetone)dipalladium(0) (32.0 mg, 0.04 mmol), BINAP (44.0 mg, 0.07 mmol) and cesium carbonate (0.2 g, 0.71 mmol) at 90°C for 17 h, to obtain 7-chloro-6-[(quinolin-6-yl-methyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron column, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm) to obtain the title compound as a white solid (50 mg, 56% overall). MS (ES+) *m/z*: 338 $(M+H)^+$.

Examples 263-266 may be prepared essentially as described in Example 262 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-

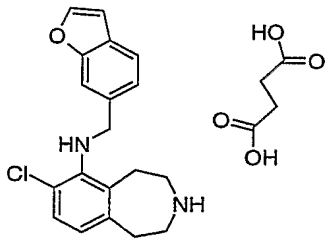
tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
263		7-Chloro-6-[(isoquinolin-3-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	63	338 $(M+H)^+$
264		7-Chloro-6-[(quinolin-3-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	35	338 $(M+H)^+$
265		7-Chloro-6-[(quinolin-2-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	20	338 $(M+H)^+$
266		7-Chloro-6-[(2-phenyl-benzoxazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Hydrochloride	15	404 $(M+H)^+$

Example 267

6-[(Benzofuran-6-ylmethyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

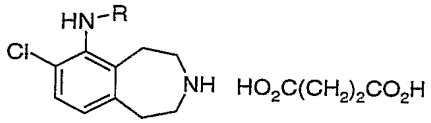


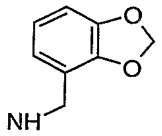
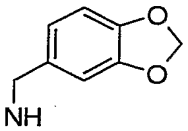
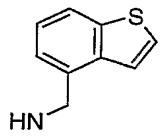
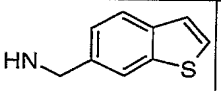
Use a method similar to the General Procedure 5-2, using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.2 g, 0.35 mmol) and 6-aminomethyl-benzofuran (0.2 g, 1.06 mmol) with tris(dibenzylideneacetone)dipalladium (0) (32.0 mg, 0.04 mmol), BINAP (88.0 mg, 0.11 mmol) and cesium carbonate (0.2 g, 0.71 mmol) at 90°C for 17 h, to obtain 6-

[(benzofuran-6-yl-methyl)-amino]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (72 mg, 46% overall). MS (ES+) *m/z*: 327 $(M+H)^+$.

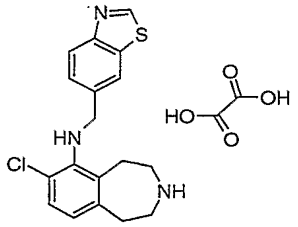
Examples 268-271 may be prepared essentially as described in Example 267 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
268		6-[(Benzo[1,3]dioxol-4-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	54	331 $(M+H)^+$
269		6-[(Benzo[1,3]dioxol-5-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	55	331 $(M+H)^+$
270		6-(Benzo[b]thiophen-4-yl-methylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	73	343 $(M+H)^+$
271		6-(Benzo[b]thiophen-6-yl-methylamino)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	48	343 $(M+H)^+$

Example 272

6-[(Benzothiazol-6-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

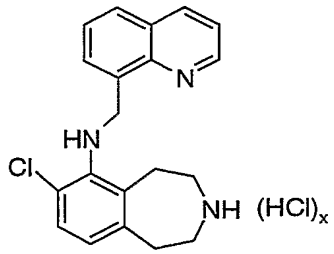


Using a method similar to the General Procedure 5-4, combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[d] azepine (0.1 g, 0.35 mmol), 6-bromomethyl-benzothiazole (80 mg, 0.35 mmol), and potassium carbonate (47.0 mg, 0.35 mmol) in anhydrous DMF (1 mL) in a sealed tube. Heat at 150°C for 3 h to obtain 6-[(benzothiazol-6-yl-methyl)-amino]-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-5 to obtain the title compound as a white solid (25 mg, 16% overall). MS (ES+) *m/z*: 344 $(M+H)^+$.

Example 273

7-Chloro-6-[(quinolin-8-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



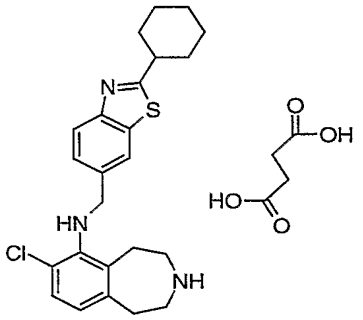
Using a method similar to the General Procedure 5-4, combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine (0.1 g, 0.35 mmol), 8-bromomethyl-quinoline (83.6 mg, 0.038 mmol), cesium carbonate (0.2 g, 0.68 mmol) and anhydrous acetonitrile (1 mL) in a sealed tube and heat at 50°C for 12 h to obtain 7-

chloro-6-[(quinolin-8-yl-methyl)-amino)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to form the hydrochloride salt and purify by reverse phase preparative HPLC [Zorbax SB-Phenyl 21.2x250 mm, 5 micron column, 22 mL/min of 0.1% HCl in water/acetonitrile (9:1 to 1:1) over 30 min, detector at 230 nm) to obtain the title compound as a white solid (13 mg, 8% overall). MS (ES+) *m/z*: 338 $(M+H)^+$.

Example 274

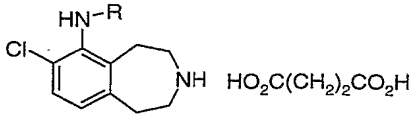
7-Chloro-6-[(2-cyclohexyl-benzothiazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

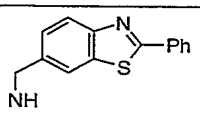
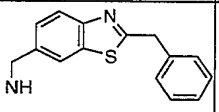
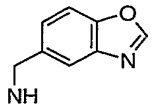


Using a method similar to the General Procedure 5-4, combine 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine (60 mg, 0.21 mmol), 6-bromomethyl-2-cyclohexyl-benzothiazole (0.1 g, 0.31 mmol), potassium carbonate (58 mg, 0.42 mmol) and anhydrous toluene (2 mL) in a sealed tube and heat at 100°C for 72 h to obtain 7-chloro-6-[(2-cyclohexyl-benzothiazol-6-yl-methyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (40 mg, 35% overall). MS (ES+) *m/z*: 427 $(M+H)^+$.

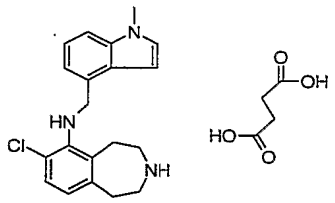
Examples 275-277 may be prepared essentially as described in Example 274 by using 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[d] azepine and the appropriate bromide. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
275		7-Chloro-6-[(2-phenyl-benzothiazol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Succinate	39	420 $(M+H)^+$
276		6-[(2-Benzyl-benzothiazol-6-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo [*d*]azepine Succinate	36	453 $(M+H)^+$
277		6-[(Benzoxazol-6-yl-methyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	7	328 $(M+H)^+$

Example 278

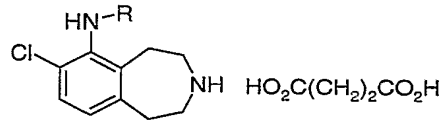
7-Chloro-6-[(1-methyl-indol-4-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

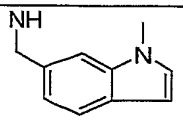
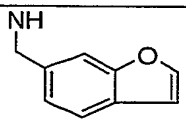


Using a method similar to the General Procedure 5-1, couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetra-hydro-1*H*-benzo[*d*]azepine (0.1 g, 0.24 mmol) with 4-aminomethyl-1-methylindole (0.1 g, 0.71 mmol) to obtain 7-chloro-6-[(1-methyl-indol-4-yl-methyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil.

Use a method similar to the General Procedure 1-1 to obtain the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-1 to obtain the title compound as a white solid (0.1 g, 91% overall). MS (ES+) *m/z*: 340 $(M+H)^+$.

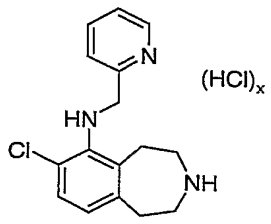
Examples 279-280 may be prepared essentially as described in Example 278 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
279		7-Chloro-6-[(1-methyl-indol-6-yl-methyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	42	340 $(M+H)^+$
280		6-[(Benzofuran-6-ylmethyl)-amino]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	327 $(M+H)^+$

Example 281

7-Chloro-6-(pyridin-2-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



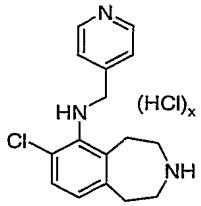
Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.17 mmol) with pyridin-2-ylmethylamine (254 mg, 2 equiv.) using palladium acetate (0.1 equiv.), BINAP (0.3 equiv.) and cesium carbonate (1.4 equiv.) in toluene (5

mL). Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1, 3:1, and 1:1) to give 7-chloro-6-(pyridin-2-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-(pyridin-2-ylmethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography followed by silica gel chromatography eluting with DCM/2M ammonia in methanol (1:0, 40:1, 20:1 and 10:1) to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to give the title compound as an off white solid (207 mg, 55% overall). MS (ES+) *m/z*: 288 $(M+H)^+$.

Example 282

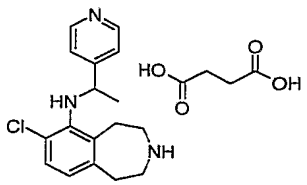
7-Chloro-6-(pyridin-4-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



may be prepared essentially as described in Example 281 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxv-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyridin-4-ylmethylamine (28% yield, and MS (ES+) 288 $(M+H)^+$).

Example 283

(±)-7-Chloro-6-[(1-pyridin-4-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

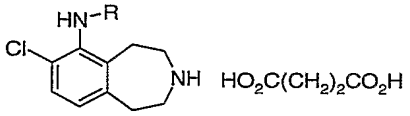


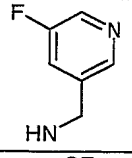
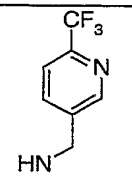
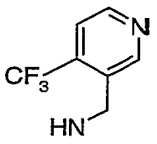
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

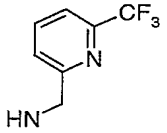
(400 mg, 0.94 mmol) and (±)-1-pyridin-4-yl-ethylamine (prepared as described in *Bull. Kor. Chem. Soc.* 1998, *19* (8), 891-893) (172 mg, 1.41 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 4:1 and 1:1) to give (±)-7-chloro-6-[(1-pyridin-4-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-1 to give the free base of the title compound (73 mg, 26%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-[(1-pyridin-4-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (73 mg, 0.243 mmol), to give the title compound (31 mg, 31%). MS (ES+) *m/z*: 302 $(M+H)^+$.

Examples 284-287 may be prepared essentially as described in Example 283 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. The yields for the Step 1 (General Procedure 5-3) and MS (ES+) data are shown in the Table below.

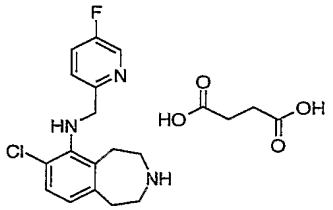


Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
284		7-Chloro-6-(5-fluoro-pyridin-3-ylmethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	88	306 $(M+H)^+$
285		7-Chloro-6-(6-trifluoromethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	83	356 $(M+H)^+$
286		7-Chloro-6-(4-trifluoromethyl-pyridin-3-yl-methylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	60	356 $(M+H)^+$

Ex.	NH-R	Compound	Yield (%)	MS (ES+) *m/z*
287		7-Chloro-6-[(6-trifluoromethyl-pyridin-2-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	84	356 $(M+H)^+$

Example 288

7-Chloro-6-[(5-fluoro-pyridin-2-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

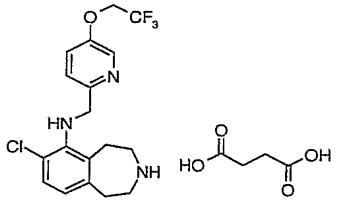


Use a method similar to the General Procedure 5-1 to couple 2-aminomethyl-5-fluoro-pyridine (230 mg, 1.8 mmol) and a solution of 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (500 mg, 1.2 mmol) in toluene (4 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) followed by SCX chromatography to give 7-chloro-6-[(5-fluoro-pyridin-2-ylmethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (302 mg, 64%). GC-MS *m/z*: 402 (M^+).

Dissolve 7-chloro-6-[(5-fluoro-pyridin-2-ylmethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (297 mg, 0.74 mmol) in ethanol (5 mL). Add 5N aqueous NaOH (10 equiv.) and stir for 1 h at ambient temperature. Concentrate *in vacuo* and purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 9:1) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 and crystallize the solid from methanol and diethyl ether. Dry the solid in a vacuum oven at 60°C overnight to obtain the title compound (181 mg, 58%). MS (ES+) *m/z*: 306 $(M+H)^+$.

Example 289

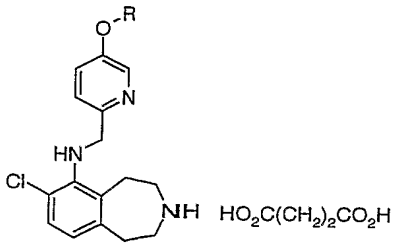
7-Chloro-6-{[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

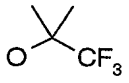
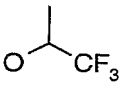


Use a method similar to the General Procedure 5-2 to couple 7-chloro-6-trifluoromethanesulfonyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (370 mg, 0.9 mmol) with 2-aminomethyl-5-(2,2,2-trifluoroethoxy)-pyridine (180 mg, 0.9 mmol) in toluene (8 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1 and 3:1) followed by SCX chromatography [pre-wash column with methanol followed by DCM, load material dissolved in DCM, then elute with DCM/2M ammonia in methanol (1:1) and concentrate *in vacuo*] to obtain 7-chloro-6-{[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine.

Use a method similar to the General Procedure 1-3 to deprotect 7-chloro-6-{[5-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethyl]-amino}-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine. Purify by chromatography on silica gel elutin with DCM/2M ammonia in methanol (99/1 to 90/10) to obtain the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound (184 mg, 42 %). MS (ES+) *m/z*: 386 $(M+H)^+$.

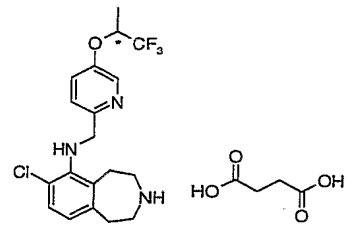
Examples 290-291 may be prepared essentially as described in Example 289 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	O-R	Compound	Yield (%)	MS (ES+) *m/z*
290		7-Chloro-6-{[5-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	48	414 $(M+H)^+$
291		(±)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin Succinate	49	400 $(M+H)^+$

Examples 292 and 293

(-)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl–ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate and (+)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

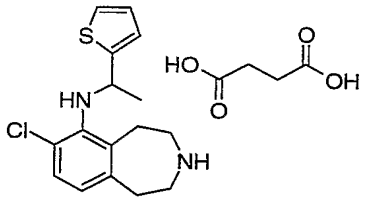


Separate the two enantiomers of (±)-7-chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate by normal phase chiral HPLC (Chiralcel OD 8x35 cm, elute with 4:1 heptane/3A-ethanol with 0.2 % DMEA). Purify each enantiomer by chromatography on silica gel eluting with DCM/2M ammonia in methanol (20:1). Use a method similar to the General Procedure 2-1 to obtain the title compounds: (-)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate

(Example 292, 75 mg, 38%), 95% ee [Chiralpak AD, 4.6x150 mm, eluent: 85/15 heptane/3A ethanol with 0.2% DMEA, 0.6 mL/min)]; MS (ES+) *m/z*: 400 $(M+H)^+$. $[\alpha]^{20}_D$ -12.1° (c 0.5, MeOH). (+)-7-Chloro-6-{[5-(2,2,2-trifluoro-1-methyl-ethoxy)-pyridin-2-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (Example 293, 72 mg, 37%), 93% ee [Chiralpak AD, 4.6x150 mm, eluent: 85/15 heptane/3A ethanol with 0.2% DMEA, 0.6 mL/min)]. MS (ES+) *m/z*: 400 $(M+H)^+$. $[\alpha]^{20}_D$ +7.4° (c 0.5, MeOH).

Example 294

(±)-7-Chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

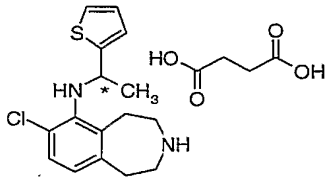


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with (±)-1-thiophen-2-yl-ethylamine (prepared as described in *J. Amer. Chem. Soc.* 1942, *64*, 477-479) (200 mg, 1.57 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to give (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (126 mg, 67%).

Use a method similar to the General Procedure 1-1, using (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (126 mg, 0.313 mmol), to give the free base of the title compound (73 mg, 77%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (73 mg, 0.241 mmol) to give the title compound (100 mg, 50% overall). MS (ES+) *m/z*: 307 $(M+H)^+$.

Example 295

(+)-7-Chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, Isomer 1

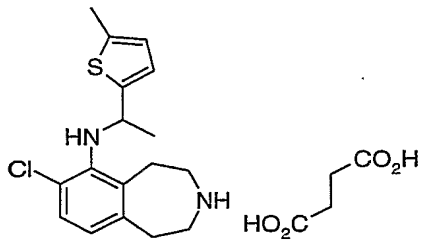


Separate the two enantiomers of (±)-7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral preparative HPLC (Chiralpak AD, 8x30 cm; eluent: 9:1 heptane/isopropanol with 0.2% DMEA; flow: 350 mL/min at 240 nm (UV), ~650 mg load] to obtain 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1, ee=100% [Analytical Column: Chiralpak AD, 4.6x250mm; eluent: 9:1 heptane/isopropanol with 0.2% DMEA; flow: 1 mL/min at 250nm (UV).

Use a method similar to the General Procedure 1-1, using 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1, to give 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[(1-thiophen-2-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (73 mg, 0.241 mmol) to give the title compound (100 mg, 98%). MS (ES+) *m/z*: 307 $(M+H)^+$. $[\alpha]^{20}_D$ +115.0° (c 0.5, MeOH).

Example 296

(±)-7-Chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

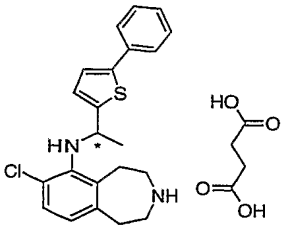


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (96 mg, 0.227 mmol) with (±)-2-(1-aminoethyl)-5-methylthiophene (48 mg, 0.34 mmol) using palladium(II) acetate (10 mg, 0.0454 mmol), BINAP (60 mg, 0.0908 mmol) and cesium carbonate (148 mg, 0.454 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 19:1) to give (±)-7-chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (47 mg, 50%). GC-MS *m/z* 416 (M^+).

Use a method similar to the General Procedure 1-2, using (±)-7-chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (47 mg, 0.113 mmol) to give (±)-7-chloro-6-[1-(5-methylthiophen-2-yl)ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (30 mg, 83%) that was used without further purification. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (36 mg, 88%). MS (ES+) *m/z*: 321 $(M+H)^+$.

Example 297

(+)-7-Chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



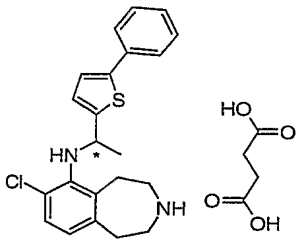
Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.328 g, 0.773 mmol) with 1-(5-phenyl-thiophen-2-yl)ethylamine Isomer 1 (0.236 g, 1.16 mmol) using palladium(II) acetate (69 mg, 0.309 mmol), tris(dibenzylideneacetone)-dipalladium(0) (142 mg, 0.155 mmol), BINAP (578 mg, 0.928 mmol) and cesium carbonate (504 mg, 1.546 mmol) in toluene (10 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 19:1) to give 7-chloro-6-[1-(5-phenyl-thiophen-

2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (89 mg, 34%).

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (89 mg, 0.186 mmol) to give 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (65 mg, 92%) as an oil that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 1 (65 mg, 0.17 mmol), to give the title compound as a white solid (58 mg, 68%). MS (ES+) *m/z*: 383 $(M+H)^+$; $[\alpha]^{20}_D$ +159.0° (c 0.5, MeOH).

Example 298

(-)-7-Chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

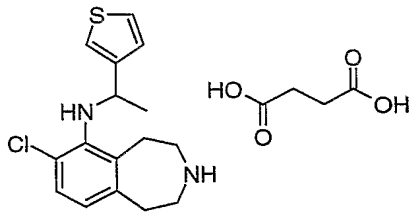


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.484 g, 1.138 mmol) with 1-(5-phenyl-thiophen-2-yl)ethylamine Isomer 2 (0.347 g, 1.71 mmol) using palladium(II) acetate (102 mg, 0.45 mmol), tris(dibenzylideneacetone)-dipalladium(0) (209 mg, 0.228 mmol), BINAP (851 mg, 1.366 mmol) and cesium carbonate (741 mg, 2.276 mmol) in toluene (12 mL). Purify by chromatography on silica gel eluting with hexane:EtOAc (1:0 and 19:1) to give 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (247 mg, 63 %).

Use a method similar to the General Procedure 1-2, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (247 mg, 0.516 mmol) to give 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (184 mg, 93%) as an oil that was used without further purification. Use a method similar to the General Procedure 2-1, using 7-chloro-6-[1-(5-phenyl-thiophen-2-yl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Isomer 2 (184 mg, 0.48 mmol) to give the title compound as a white solid (200 mg, 83%). MS (ES+) *m/z*: 383 $(M+H)^+$; $[\alpha]^{20}_D$ -196.5° (c 0.5, MeOH).

Example 299

(±)-7-Chloro-6-[(1-thiophen-3-yl-ethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

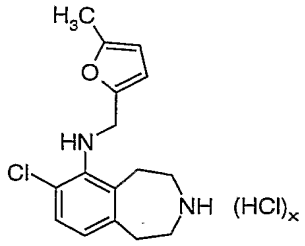


Use a method similar to the General Procedure 5-3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.47 mmol) with (±)-1-thiophen-3-yl-ethylamine (prepared as described in *J. Heterocycl. Chem.* 1988, *25*, 1571-1581) (90 mg, 0.70 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1) to give (±)-7-chloro-6-(1-thiophen-3-yl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 53%).

Use a method similar to the General Procedure 1-1, using (±)-7-chloro-6-(1-thiophen-3-yl-ethylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.248 mmol), to give the free base of the title compound (74 mg, 98%). Use a method similar to the General Procedure 2-1, using (±)-7-chloro-6-(1-thiophen-3-yl-ethylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (74 mg, 0.242 mmol) to give the title compound (108 mg, 54% overall). MS (ES+) *m/z*: 307 $(M+H)^+$.

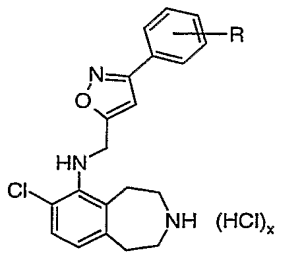
Example 300

7-Chloro-6-[(5-methylfuran-2-ylmethyl)-amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Combine 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 0.24 mmol), 2-(di-*tert*-butylphosphino)-biphenyl (6.8 mg, 0.023 mmol), tris(dibenzylideneacetone)dipalladium (11 mg, 0.012 mmol) and potassium phosphate (70 mg, 0.33 mmol) in a pressure tube and degas. Dissolve the mixture in dry toluene (2 mL) and degas. Add a solution of 5-methylfurfurylamine (30 mg, 0.27 mmol) in toluene (1 mL) and degas. Stir at 90°C for 24 h. Cool to ambient temperature, dilute with ethyl ether and filter through Celite®. Concentrate and purify by chromatography on silica gel eluting with hexane/EtOAc (20:1). Remove the solvent and add 7M ammonia in methanol (4 mL). Stir at ambient temperature for 24 h. Concentrate and purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-2 to obtain the title compound as a solid (56 mg, 66%). MS (ES+) *m/z*: 291 $(M+H)^+$.

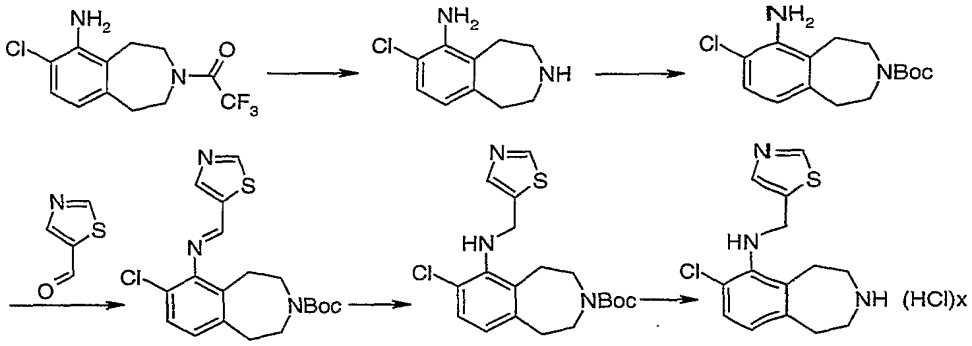
Examples 301-302 may be prepared essentially as described in Example 300 by using 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
301	4-Cl	7-Chloro-6-{[3-(4-chlorophenyl)-isoxazol-5-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	30	389 $(M+H)^+$
302	4-OMe	7-Chloro-6-{[3-(4-methoxyphenyl)-isoxazol-5-ylmethyl]-amino}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	54	384 $(M+H)^+$

Example 303

7-Chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Thiazole-5-carbaldehyde: Add DMSO slowly to a solution of oxalyl chloride (1.6 g, 13 mmol) in anhydrous DCM (30 mL) under nitrogen at –78 °C and stir for 10 min. Add dropwise a solution of 5-hydroxymethylthiazole (1.15 g, 10 mmol) in DCM (10 mL) and stir the mixture for 40 min. Add triethylamine and stir for 5 min and then quench the reaction with water. Extract the mixture three times with ether, combine the organic extracts, wash with brine, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (2:5) to give thiazole-5-carbaldehyde (337 mg, 29%).

3-(*tert*-Butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyleneamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-amino-7-chloro-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (285 mg, 0.97 mmol) in methanol (10 mL). Add 7N ammonia in methanol (10 mL) and stir overnight at ambient temperature. Concentrate *in vacuo* and dissolve the residue in THF (10 mL). Add saturated aqueous $NaHCO_3$ (5 mL)

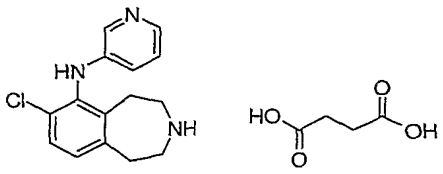
and di-*tert*-butyl-dicarbonate (254 mg, 1.16 mmol). Stir the reaction mixture at ambient temperature for 4 h. Dilute the mixture with water, extract three times with EtOAc, combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo* to give crude material. Mix thiazole-5-carbaldehyde (165 mg, 1.45 mmol) with above crude residue (0.97 mmol, assuming 100% conversion), acetic acid (87 mg, 1.45 mmol) and 1,2-dichloroethane (10 mL). Stir at ambient temperature for 20 min. Add sodium triacetoxyborohydride and stir under nitrogen overnight. Quench the reaction with saturated aqueous $NaHCO_3$, separate the organic layer and extract the aqueous layer three times with DCM. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to afford the desired intermediate as a yellow oil (228 mg, 60% three steps). MS (ES+) *m/z*: 392 $(M+H)^+$.

3-(*t*-Butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 3-(*t*-butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyleneamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (228 mg, 0.58 mmol) in methanol (10 mL), add sodium borohydride (263 mg, 7 mmol) and reflux for 28 h. Cool to ambient temperature, dilute with EtOAc and add slowly water. Separate the organic layer, extract the aqueous layer three times with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc/hexane (1:3) to give the desired intermediate as a colorless oil (134 mg, 58%). MS (ES+) *m/z*: 394 $(M+H)^+$.

7-Chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: Use a method similar to the General Procedure 1-6 to deprotect 3-(*tert*-butoxycarbonyl)-7-chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (134 mg, 0.34 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to give 7-chloro-6-(thiazol-5-ylmethyl-amino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (90 mg, 90%). MS (ES+) *m/z*: 294 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to obtain the title compound.

Example 304

7-Chloro-6-[(3-pyridyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

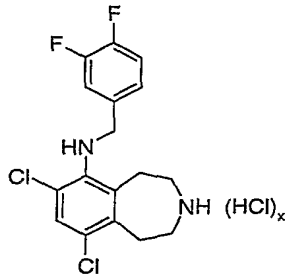


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.7 mmol) with 3-aminopyridine (75 mg, 0.85 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give 7-chloro-6-[(3-pyridyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an off-white solid (20 mg, 8%). MS (ES+) *m/z*: 370 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-6-[(3-pyridyl)amino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (20 mg, 0.05 mmol). Purify by SCX chromatography to give 7-chloro-6-[(3-pyridyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (15 mg, 99%). Use a method similar to the General Procedure 2-1, using 7-chloro-6-[(3-pyridyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (15.1 mg, 0.05 mmol), to give the title compound as a light yellow solid (20 mg, 97%). MS (ES+) *m/z*: 319 $(M+H)^+$.

Example 305

7,9-Dichloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



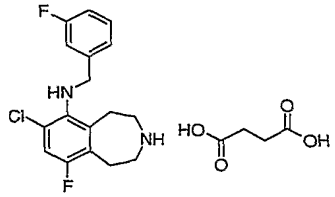
Dissolve 7-dichloro-6-(3,4-difluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.36 mmol) in anhydrous toluene (20 mL). Add *N*-chlorosuccinimide (140 mg, 1 mmol) and heat at 60°C for 4 h. Cool to room

temperature, pour reaction mixture into water (250 mL) and extract with EtOAc (3x50 mL). Wash combined organic extracts with water, brine, dry over Na_2SO_4, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give 7,9-dichloro-6-(3,4-difluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (110 mg, 67%). MS (ES+) *m/z*: 453 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7,9-dichloro-6-(3,4-difluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (120 mg, 0.26 mmol). Purify by SCX chromatography to give 7,9-dichloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (81 mg, 88%). Use a method similar to the General Procedure 2-2, using 7,9-dichloro-6-(3,4-difluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (75 mg, 0.21 mmol), to give the title compound as a yellow gum (80 mg, 96%). MS (ES+) *m/z*: 357 $(M+H)^+$.

Example 306

7-Chloro-9-fluoro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



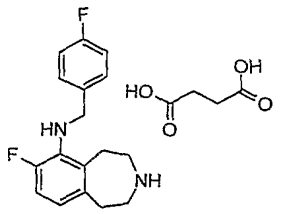
Use a method similar to the General Procedure 5-1 to couple 7-chloro-9-fluoro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (130 mg, 0.3 mmol) with 3-fluorobenzylamine (100 □L, 0.89 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 and 4:1) followed by SCX chromatography to give 7-chloro-9-fluoro-6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (35 mg, 28%). MS (ES+) *m/z*: 401 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-chloro-9-fluoro-6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (32 mg, 0.08 mmol). Purify by SCX chromatography to give 7-chloro-9-fluoro-6-(3-

fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (10 mg, 45%). Use a method similar to the General Procedure 2-1, using 7-chloro-9-fluoro-6-(3-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (10 mg, 0.033 mmol), to give the title compound as a light yellow solid (14 mg, 97%). MS (ES+) *m/z*: 323 $(M+H)^+$.

Example 307

7-Fluoro-6-(4-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

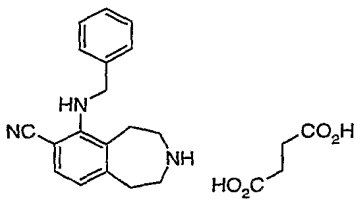


Use a method similar to the General Procedure 5-1 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (250 mg, 0.61 mmol) with 4-fluorobenzylamine (92 mg, 1.2 equiv.) using palladium(II) acetate (0.1 equiv.), BINAP (0.3 equiv.) and cesium carbonate (1.4 equiv.) in toluene (5 mL). Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1, 5:1, 3:1 and 1:1) to give 7-fluoro-6-(4-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil.

Use a method similar to the General Procedure 1-3 to deprotect 7-fluoro-6-(4-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound. Use a method similar to the General Procedure 2-1 to give the title compound as an off white solid (14 mg, 6%). MS (ES+) *m/z*: 289 $(M+H)^+$.

Example 308

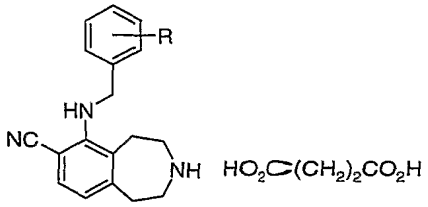
6-Benzylamino-7-cyano-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the General Procedure 5-1 to couple 7-cyano-3-(2,2,2-trifluoroacetyl)-6- trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (125 mg, 0.3 mmol) with benzylamine (0.1 mL, 0.9 mmol) using palladium(II) acetate (7 mg, 0.03 mmol), BINAP (37 mg, 0.06 mmol) and cesium carbonate (137 mg, 0.4 mmol) in toluene (3 mL). Purify by chromatography on silica gel eluting with heptane/EtOAc (4:1 to 1:1) to give 6-benzylamino-7-cyano-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (60 mg, 54%). MS (ES+) *m/z*: 374 $(M+H)^+$.

Use a method similar to the General Procedure 1-2, using 6-benzylamino-7-cyano-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (56 mg, 0.15 mmol), to give 6-benzylamino-7-cyano-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (38 mg, 93%). MS (ES+) *m/z*: 278 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a white powder (39 mg, 71%). MS (ES+) *m/z*: 278 $(M+H)^+$.

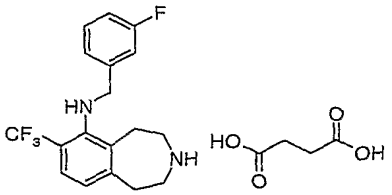
Examples 309-310 may be prepared essentially as described in Example 308 by using 7-cyano-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriate amine. Overall yields and MS (ES+) data are shown in the Table below.



Ex.	R	Compound	Yield (%)	MS (ES+) *m/z*
309	4-F	7-Cyano-6-(4-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	46	296 $(M+H)^+$
310	2-F	7-Cyano-6-(2-fluorobenzylamino)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	43	296 $(M+H)^+$

Example 311

6-(3-Fluorobenzylamino)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

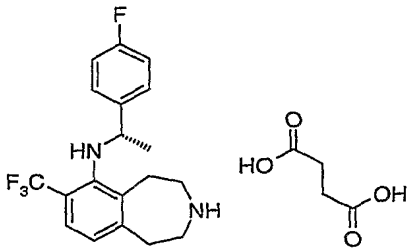


Use a method similar to the General Procedure 5-1 to couple 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (110 mg, 0.24 mmol) and 3-fluorobenzyl amine (90 μL, 0.7 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) followed by SCX chromatography to give 6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (55 mg, 53%). MS (ES+) *m/z*: 435 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 6-(3-fluorobenzylamino)-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (55 mg, 0.13 mmol). Purify by SCX chromatography to give 6-(3-fluorobenzylamino)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (34 mg, 81%). Use a method similar to the General Procedure 2-1 to give the title compound as an off-white solid (33 mg, 72%). MS (ES+) *m/z*: 339 $(M+H)^+$.

Example 312

(*S*)-(-)-6-[1-(4-Fluorophenyl)-ethylamino]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

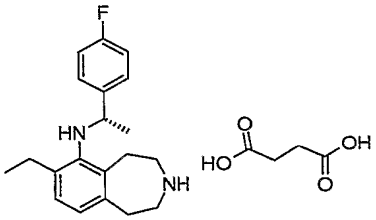


Use a method similar to the General Procedure 5-3 to couple 3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (430 mg, 0.94 mmol) with (*S*)-1-(4-fluorophenyl)ethylamine (195 mg, 1.40 mmol). Purify by chromatography on silica gel eluting with EtOAc/hexane (1:8) to give (*S*)-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (279 mg, 65%). MS (ES+) *m/z*: 449 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (*S*)-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (279 mg, 0.62 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (94:6) to obtain (*S*)-6-[1-(4-fluorophenyl)-ethylamino]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (190 mg, 87%). MS (ES+) *m/z*: 353 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound. $[\alpha]^{20}_D$ -96.7° (c 0.5, MeOH).

Example 313

(*S*)-7-Ethyl-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



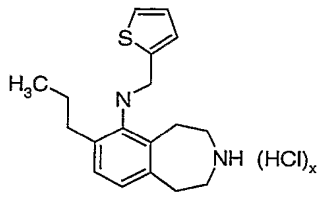
Use a method similar to the General Procedure 5-3 to couple 7-ethyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (335 mg, 0.8 mmol) and (*S*)-1-(4-fluorophenol)ethyl amine (557 mg, 4.0 mmol). Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 17:3) to give (*S*)-7-ethyl-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (127 mg, 39%). MS (ES+) *m/z*: 409 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect (*S*)-7-ethyl-6-[1-(4-fluorophenyl)-ethylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-

benzo[*d*]azepine. Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (93:7) to give (*S*)-7-ethyl-6-[1-(4-fluorophenyl)-ethylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (70 mg, 72%). MS (ES+) *m/z*: 313 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Example 314

7-Propyl-6-[(2-thienyl)methylamino]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 5-1 to couple 7-propyl-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-(aminomethyl)-thiophene. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 and 4:1) to give 7-propyl-6-[(2-thienyl)methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow solid. MS (ES+) *m/z*: 397 $(M+H)^+$.

Use a method similar to the General Procedure 1-1 to deprotect 7-propyl-6-[(2-thienyl)methylamino]-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Purify by SCX chromatography to give the free base of the title compound as a yellow oil. Use a method similar to the General Procedure 2-2 to give the title compound as a light yellow solid. MS (ES+) *m/z*: 301 $(M+H)^+$.

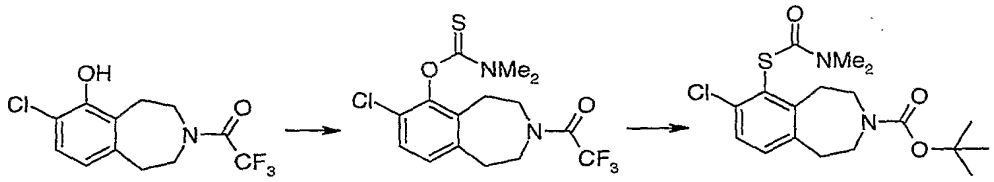
General Procedure 7

Dissolve the appropriate substituted 3-*tert*-butoxycarbonyl-6-dimethylcarbamoyl-thio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 equiv) in methanol (0.1-0.2 M solution). Add potassium hydroxide (32 equiv.) and heat the mixture at 50°C for 2-8 h. Cool the reaction to ambient temperature and add the appropriate halide (1.0-5.0 equiv.). Stir the mixture at ambient temperature for 0.5-16 h. Remove the solvent *in vacuo* and partition the residue between DCM and water. Extract the aqueous phase with DCM, combine the

organic extracts, dry over Na_2SO_4, filter and concentrate. Purify by chromatography in silica gel eluting with hexane/EtOAc mixtures to obtain the desired compound.

Preparation 172

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



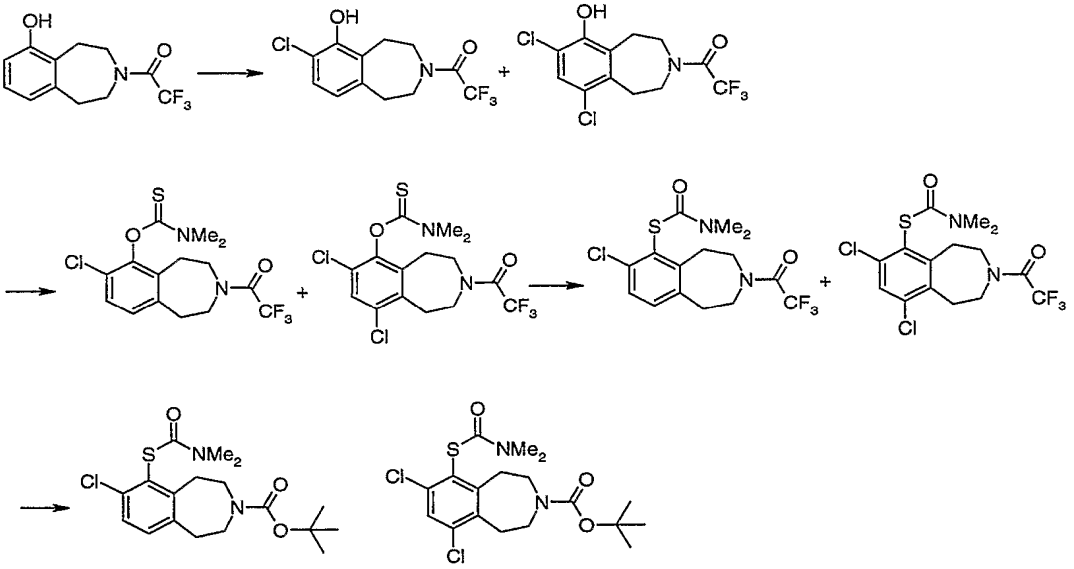
7-Chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Place 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (64.3 g, 219 mmol) in acetone (450 mL) and water (200 mL) with K_2CO_3 (91.8 g, 664 mmol) and dimethylthiocarbamoyl chloride (31.5 g, 255 mmol). Stir at ambient temperature for 1.25 h. Add additional dimethylthiocarbamoyl chloride (3 g, 24 mmol) and stir for an additional 1.75 h at ambient temperature. Add more dimethylthiocarbamoyl chloride (0.7 g, 5.7 mmol) and water (150 mL) to the mixture and stir for 0.5 h at ambient temperature. Slowly add water (500 mL) to the reaction over 2 h to promote crystallization and stir the resulting slurry at ambient temperature for 1.5 h. Collect the solid by filtration to give the desired intermediate (76 g, 91%).

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 7-chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (155 g, 407 mmol) in diphenyl ether (1500 mL) and heat to 250°C for 2.5 h. Cool the reaction and dilute with methanol (308 mL). Add 1N aqueous NaOH (616 mL) and stir at 60°C for 4 h. Cool the reaction to ambient temperature and extract between DCM (3 x 500 mL) and water (500 mL). Combine the organic extracts and add to 1N aqueous HCl (1 L). Stir the reaction at ambient temperature for 0.25 h then wash with hexane (5 x 400 mL). Adjust the pH of the aqueous layer to 7.0 with 5N aqueous NaOH and mix the aqueous solution with DCM (2.5 L). Cool the mixture in an ice bath and add K_2CO_3 (169 g, 1221 mmol) and di-*t*-

butyl dicarbonate (67.5 g, 390 mmol) and stir the reaction at ambient temperature for 0.5 h. Add di-*t*-butyl dicarbonate (16.35 g, 75 mmol) and stir for 0.3 h at ambient temperature. Add di-*t*-butyl dicarbonate (0.1 g, 0.46 mmol) and stir for 0.25 h at ambient temperature. Concentrate the mixture *in vacuo* to remove the volatiles and warm to 45°C. Seed the mixture with a small amount of the title compound and stir for 1 h at 45°C. Cool the reaction in an ice bath and stir for an additional 2 h. Collect the resultant solid by filtration and rinse with cold hexane (100 mL). Concentrate the filtrate *in vacuo*, recrystallize from DCM/heptane, and isolate the solids by filtration. Combine the solids and dry *in vacuo* to give the title compound as a white crystalline solid (142 g, 91%). MS (ES+) *m/z* 385 $(M+H)^+$.

Preparation 173

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine:

To a solution of 6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.961 g, 3.71 mmol) in toluene (30 mL) at 70 °C, add diisobutylamine (52 µL, 0.30 mmol) followed by slow addition of neat sulfuryl chloride (343 µL,

4.27 mmol). Stir for 1 h at 70 °C and concentrate *in vacuo*. Dilute the residue with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to afford a 4:1 mixture of 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (1.07 g, 98%).

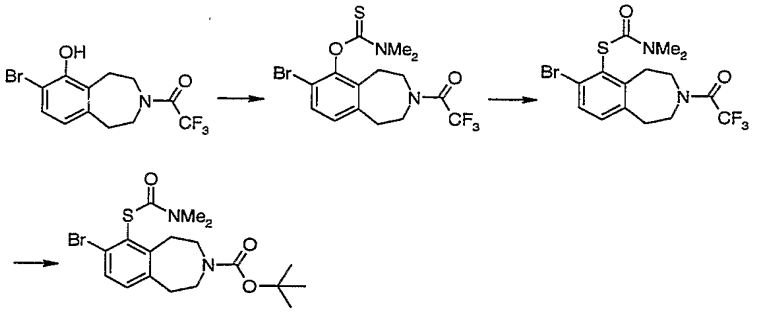
7-Chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a mixture of 4:1 7-chloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.513 g, 1.75 mmol) in anhydrous dioxane (10 mL) under nitrogen, add dimethyl thiocarbamoyl chloride (0.432 g, 3.50 mmol), 4-dimethylaminopyridine (21 mg, 0.18 mmol) and triethylamine (731 μL, 5.24 mmol) and heat under reflux overnight. Cool the reaction mixture to ambient temperature and dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (17:1) to afford a mixture of 4:1 7-chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.64 g, 95%)

7-Chloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat the mixture of 4:1 7-chloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.630 g, 1.66 mmol) in diphenyl ether (4.5 mL) at 250 °C for 4 h under nitrogen. Cool to ambient temperature. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3) to give a mixture of 4:1 7-chloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (0.54 g, 85%).

3-*tert*-Butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To the mixture of 4:1 7-chloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 7,9-dichloro-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (0.536 g, 1.47 mmol) in methanol (7 mL), add aqueous potassium carbonate (0.812 g, 5.88 mmol in 1.5 mL of water). Stir for 5 h at ambient temperature, add di-*tert*-butyl dicarbonate (418 mg, 1.91 mmol) and stir for an additional 30 min. Dilute with EtOAc and water. Separate the layers and extract the aqueous layer three times with EtOAc. Dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3) to give a mixture of 4:1 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid (0.52 g, 96%).

Preparation 174

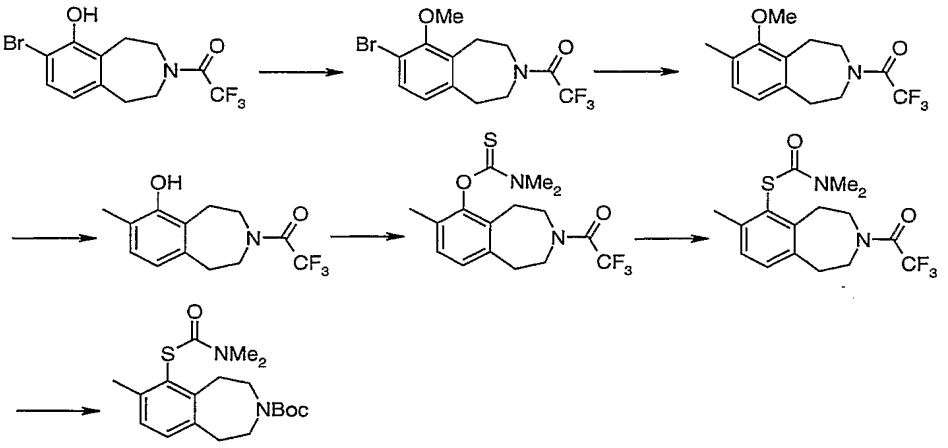
7-Bromo-3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



Use a method similar to the Preparation 172, using 7-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound.

Preparation 175

3-*tert*-Butoxycarbonyl-6-dimethylcarbamoylthio-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Bromo-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium carbonate (10.214 g, 73.9 mmol) to a solution of 7-bromo-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5.0 g, 14.8 mmol) in acetone (50 mL) and stir for 10 min. Add methyl iodide (4.2 g, 1.5 mL, 29.6 mmol) and stir the mixture overnight at room temperature. Remove the solvent *in vacuo* and partition the residue between water and DCM. Extract the aqueous phase twice with DCM. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo* to obtain the desired intermediate as a solid (5.15 g, 99%). MS (ES+) *m/z*: 352 $(M+H)^+$.

6-Methoxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium carbonate (5.65 g, 40.91 mmol), tetrakis(triphenylphosphine)palladium (1.576 g, 1.363 mmol) and trimethylboroxine (2.053 g, 2.3 mL, 16.35 mmol) to a solution of 7-bromo-6-methoxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (4.8 g, 13.63 mmol) in dimethylformamide (40 mL) under nitrogen. Heat the mixture to 115°C for 6 h. Add water and extract the aqueous phase twice with EtOAc. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 19:1) to obtain the desired intermediate as a solid (3.23 g, 83%). GC-MS *m/z* 287 (M^+).

6-Hydroxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add borontribromide (21.6 mL, 1.0 M solution in DCM) to a solution of 6-methoxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.1 g, 10.8 mmol) in DCM (200 mL) at 0°C under nitrogen. Warm to room temperature and stir overnight. Dilute with DCM and wash with water. Dry the organic layer over Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a solid (2.74 g, 93%). MS (ES+) *m/z*: 274 $(M+H)^+$.

6-Dimethylthiocarbamoyloxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-hydroxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 3.66 mmol) in acetone (50 mL). Add potassium carbonate (1.517 g, 10.98 mmol) and dimethylthiocarbamoyl chloride (0.904 g, 7.32 mmol). Heat the mixture at reflux overnight. Remove the solvent *in vacuo* and partition the residue between water and DCM. Dry the organic phase over Na_2SO_4, filter and concentrate. Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 9:1) to obtain the desired intermediate as a solid (1.18 g, 90%). MS (ES+) *m/z*: 361 $(M+H)^+$.

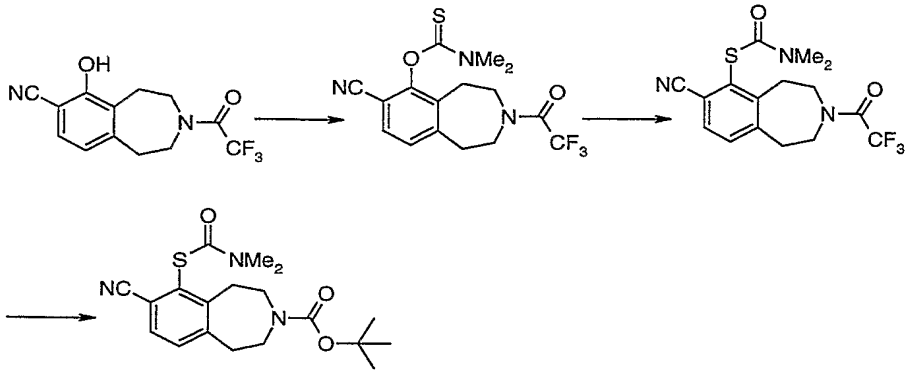
6-Dimethylcarbamoylthio-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-dimethylthiocarbamoyloxy-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.15 g, 3.19 mmol) in diphenyl ether (20 mL) and heat to 265°C for 3 h in a sealed tube. Cool the reaction to room temperature. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1 and 7:3) to obtain the desired intermediate as a solid (1.10 g, 96%). MS (ES+) *m/z*: 361 $(M+H)^+$.

3-*tert*-Butoxycarbonyl-6-dimethylcarbamoylthio-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-dimethylcarbamoylthio-7-methyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.048 g, 2.9 mmol) in methanol (40 mL). Add a solution of potassium carbonate (1.6 g, 11.6 mmol) in water (10 mL). Stir at room temperature overnight. Remove the solvent and partition the residue between water and

DCM. Extract the aqueous phase twice with DCM. Combine the organic extracts, dry over Na_2SO_4, filter and concentrate. Dissolve the residue (0.756 g, 2.86 mmol) in DCM (50 mL). Add triethylamine (0.579 g, 0.8 mL, 2.0 equiv) and di-*tert*-butyl dicarbonate (0.624 g, 2.86 mmol) and stir at room temperature overnight. Dilute with DCM and wash with water. Dry the organic phase over Na_2SO_4, filter and concentrate to obtain the title compound as foam (1.038 g, 99%). MS (ES+) *m/z*: 264 $(M+H\text{-}Boc)^+$.

Preparation 176

3-*tert*-Butoxycarbonyl-7-cyano-6-dimethylcarbamoylsulfanyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Cyano-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add dimethylthiocarbamoyl chloride (197 mg, 1.58 mmol) to a stirred solution of 7-cyano-6-hydroxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (150 mg, 0.53 mmol), DMAP (6 mg, 0.05 mmol) and dry triethylamine (300 µL) in dry 1,4-dioxane (5 mL) under an atmosphere of nitrogen and heat at 120 °C for 6 h. Cool and continue stirring for 2 days at ambient temperature. Dilute with EtOAc, wash with 1N aqueous HCl, water, saturated aqueous Na_2CO_3 and brine. Dry over $MgSO_4$ then concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc:heptane (0:1 to 3:10) to give the desired intermediate as a white solid (158 mg, 81%).

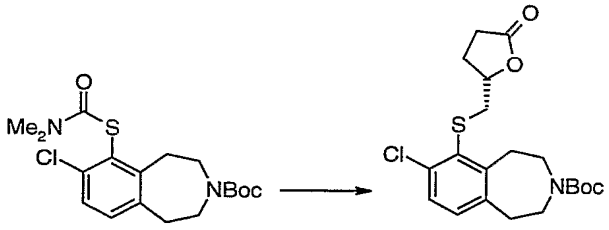
7-Cyano-6-dimethylcarbamoylsulfanyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a round bottom flask containing a solution of 7-cyano-6-dimethylthiocarbamoyloxy-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (786 mg, 2.12 mmol) in diphenyl ether (21 mL) in a preheated oil bath at

230°C for 2 h. Cool and purify by chromatography on silica gel eluting with EtOAc:heptane (0:1 to 1:1) to give the desired intermediate as a yellow foam (740 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (d, 1H), 7.36-7.30 (d, 1H), 3.88-3.68 (m, 4H), 3.34-3.03 (m, 10H).

3-*tert*-Butoxycarbonyl-7-cyano-6-dimethylcarbamoylsulfanyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add potassium carbonate (4.13 g, 30 mmol) to a stirred solution of 7-cyano-6-dimethylcarbamoylsulfanyl-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (740 mg, 2.0 mmol) in methanol (40 mL)/water (15 mL) and stir for 1.5 h. Add DCM (10 mL), di-*tert*-butyl dicarbonate (480 mg, 2.2 mmol) and stir at ambient temperature for 3 days. Concentrate *in vacuo* and dilute with DCM, wash with water and extract with DCM. Combine the organic layers, wash with brine, dry over $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with EtOAc:heptane (0:1 to 1:1) to give the title compound as a colourless foam (370 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* 8 Hz, 1H), 7.29 (d, *J* 8 Hz, 1H), 3.69-3.48 (m, 4H), 3.26-3.02 (m, 10H), 1.45 (s, 9H).

Preparation 177

(*S*)-3-*tert*-Butoxycarbonyl-7-chloro-6-(5-oxo-tetrahydro-furan-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

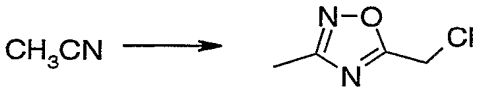


To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine (137 mg, 0.356 mmol) in methanol (2 mL) add potassium hydroxide pellets (640 mg, 11.4 mmol) and heat for 3 h at 50 °C. Cool to ambient temperature, add saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Dissolve the crude thiophenol thus obtained in dry DMF (2 mL), and add with stirring sodium hydride (18 mg, 0.713 mmol,

95% dispersion), followed by (*S*)-(+)-dihydro-5-(*p*-tolylsulfonyloxymethyl)-2-(3*H*)-furanone (144 mg, 0.533 mmol). Continue stirring overnight at ambient temperature, then dilute cautiously with EtOAc and cold saturated aqueous NH_4Cl. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:3) to give the title compound as a colorless oil.

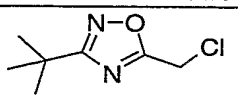
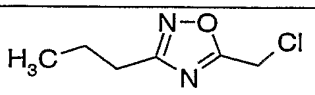
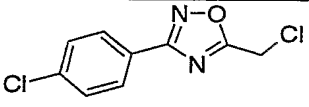
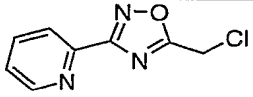
Preparation 178

5-Chloromethyl-3-methyl-[1,2,4]oxadiazole



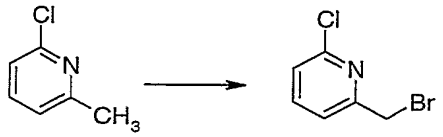
Add with stirring hydroxylamine (50 % in water, 25.0 mL, 0.380 mol) to a solution of acetonitrile (5.0 mL, 95.0 mmol) and ethanol (500 mL). Heat at 70 °C for 18 h. Concentrate *in vacuo* to provide crude *N*-hydroxyacetamidine (7.0 g, 100 %). Add slowly with stirring vinyl chloroacetate (2.1 mL) to *N*-hydroxyacetamidine (*J. Org. Chem.* 1971, *36*, 1306-1307) (1.00 g, 13.5 mmol) and heat at 90 °C for 5 h. Cool to ambient temperature, dilute with DCM, wash with aqueous 1N aqueous NaOH, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the title compound (904 mg, 50%).

The compounds of Preparation 179-182 were prepared essentially as described in Preparation 178.

Prep.	Structure	Compound
179		3-*tert*-Butyl-5-chloromethyl-[1,2,4]oxadiazole
180		5-Chloromethyl-3-propyl-[1,2,4]oxadiazole
181		5-Chloromethyl-3-(4-chloro-phenyl)-[1,2,4]oxadiazole
182		2-(5-Chloromethyl-[1,2,4]oxadiazol-3-yl)-pyridine

Preparation 183

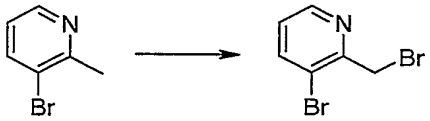
2-Bromomethyl-6-chloropyridine



Heat a mixture of 2-chloro-6-methylpyridine (5.46 g, 42.8 mmol), NBS (8.38 g, 47.08 mmol), and benzoyl peroxide (500 mg, 2.06 mmol) in carbon tetrachloride (80 mL) for 20 h at 85 °C. Cool to ambient temperature, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/toluene (4:3) to provide the title compound as a white solid (3.64 g, 41%).

Preparation 184

3-Bromo-2-bromomethyl-pyridine



Heat a mixture of 3-bromo-2-methylpyridine (*J. Med. Chem.* 1987, *30*, 871-880) (2.7 g, 15.8 mmol), NBS (3.10 g, 17.42 mmol), and benzoyl peroxide (190 mg, 0.78 mmol) in carbon tetrachloride (50 mL) overnight at 85 °C. Cool to ambient temperature, filter, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with toluene to provide the title compound as a white solid (1.81 g, 45%).

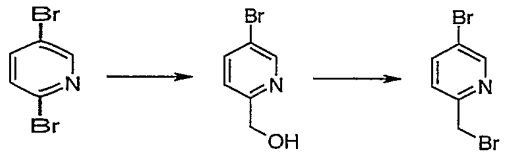
Preparation 185

2-Bromo-6-bromomethyl-pyridine

Use a method similar to the Preparation 184, using 2-bromo-6-methylpyridine, to give the title compound.

Preparation 186

5-Bromo-2-bromomethylpyridine

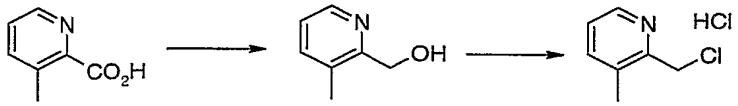


2-Hydroxymethyl-5-bromopyridine: Dissolve 2,5-dibromopyridine (10 g, 42 mmol) in toluene (500 mL) and cool to −78 °C. Add 2.5M *n*-butyllithium in hexane (20.3 mL, 50.6 mmol) and stir the mixture for 7 h at the same temperature. Add DMF (4.2 mL, 54.87 mmol) and stir for 1 h. Warm the solution to 0 °C and add sodium borohydride (3.2 g, 84.42 mmol). Stir the mixture at ambient temperature for 3 h. Dilute with EtOAc and saturated aqueous NH_4Cl. Separate the layers and extract the aqueous layer three times with EtOAc. Dry over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Recrystallization from hexane/EtOAc (9:1) gives the desired intermediate as a white solid (5.3 g, 66%).

5-Bromo-2-bromomethyl-pyridine : Dissolve 2-hydroxymethyl-5-bromopyridine (5.21 g, 27.7 mmol) in 48% aqueous hydrobromic acid (20 mL). Heat the mixture at 150 °C for 2 h. Cool to ambient temperature and remove excess hydrobromic acid under vacuum. Dilute with water, add cautiously saturated aqueous $NaHCO_3$ and extract three times with EtOAc. Dry over anhydrous Na_2SO_4, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as pink oil (6.0 g, 87%) that crystallizes in the freezer.

Preparation 187

2-Chloromethyl-3-methylpyridine Hydrochloride



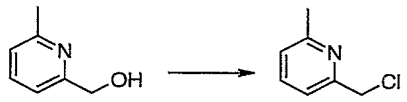
2-Hydroxymethyl-3-methylpyridine: Heat a mixture of 3-methylpicolinic acid (1.0 g, 7.3 mmol), potassium carbonate (4.1 g, 29.7 mmol), and iodomethane (4.4 g, 31.0 mmol) in acetone (35 mL) overnight under reflux. Filter, wash the residue with EtOAc, and concentrate *in vacuo*. Pass through a short plug of silica gel eluting with hexane/EtOAc (1:1) to provide 2-methoxycarbonyl-3-methylpyridine as a pale yellow liquid (630 mg, 57%). To a solution of 2-methoxycarbonyl-3-methylpyridine in anhydrous THF (10 mL)

at 0 °C, add with stirring a solution of 1M lithium aluminum hydride in THF (5 mL, 5 mmol), and continue stirring for 30 min at 0 °C. Allow the mixture to warm to ambient temperature and quench cautiously with 0.5M aqueous NaOH. Heat the mixture at 60 °C for 40 min, cool to ambient temperature, extract with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:3) to give the desired intermediate (90 mg, 18%).

2-Chloromethyl-3-methylpyridine hydrochloride: To 2-hydroxymethyl-3-methylpyridine (90 mg, 0.73 mmol) in dry DCM (10 mL) at ambient temperature, add with stirring thionyl chloride (0.53 mL, 7.3 mmol). Continue stirring overnight, concentrate *in vacuo*, and azeotrope three times with chloroform. Triturate the residue with dry ether, filter, and dry under vacuum to obtain the title compound as a beige solid (130 mg, 100%).

Preparation 188

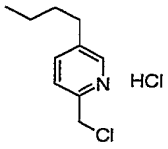
2-Chloromethyl-6-methylpryidine



Add with stirring a solution of thionyl chloride (0.77 mL, 10.6 mmol) in dry DCM (20 mL) to 2-hydroxymethyl-6-methylpyridine (1.0 g, 8.12 mmol) in dry DCM (20 mL) at 0 °C. Continue stirring at 0 °C for 1.25 h. Quench with isopropanol and concentrate *in vacuo*. Dissolve the residue in DCM, wash with saturated aqueous $NaHCO_3$, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give the title compound. MS (ES+) *m/z* 142 $(M+H)^+$.

Preparation 189

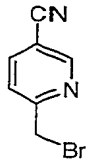
5-Butyl-2-chloromethylpyridine Hydrochloride



Use a method similar to the Preparation 187, using fusaric acid, to give the title compound. MS (APCI+) *m/z* 184 $(M+H)^+$.

Preparation 190

6-Bromomethylnicotinonitrile



Use a method similar to the Preparation 184, using 5-cyano-2-methylpyridine, to give the title compound.

Preparation 191

5-Bromomethyl-pyridine-2-carbonitrile

Use a method similar to the Preparation 184, using 5-methyl-picolinonitrile (*J. Chem. Soc.* 1962, 2637-2658), to give the title compound.

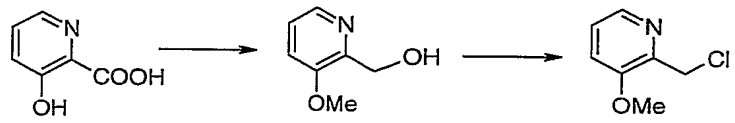
Preparation 192

2-Chloromethyl-3-trifluoromethylpyridine Hydrochloride

Use the chlorination method described in Preparation 187, using 2-hydroxymethyl-3-trifluoromethylpyridine, to give the title compound. MS (APCI+) *m/z* 196 $(M+H)^+$.

Preparation 193

2-Chloromethyl-3-methoxypyridine

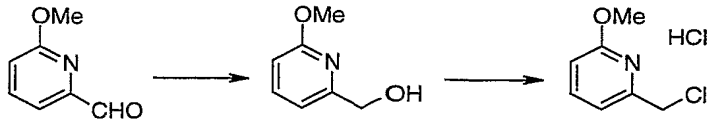


2-Hydroxymethyl-3-methoxypyridine: Heat a mixture of 3-hydroxypicolinic acid (5.3 g, 38 mmol), potassium carbonate (15.8 g, 114 mmol), and iodomethane (9.6 mL, 153 mmol) in acetone (100 mL) and DMF (10 mL) overnight at 60°C. Cool the reaction mixture to ambient temperature, pour into brine, extract three times with ethyl ether, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Pass through a short plug of silica gel eluting with ether to provide 3-methoxy-2-methoxycarbonylpyridine as a pale yellow liquid (6.3 g, 100%). To a solution of 3-methoxy-2-methoxycarbonyl-pyridine (2.34 g, 14.0 mmol) in dry THF (25 mL) add slowly with stirring a solution of 1M lithium aluminum hydride in THF (10 mL, 10 mmol) and continue stirring overnight at ambient temperature. Quench cautiously with sodium sulfate decahydrate, filter under suction and rinse the solids with additional THF. Concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (3:1) to provide the desired intermediate as a white solid (350 mg, 18%).

2-Chloromethyl-3-methoxypyridine: Use a method similar to the Preparation 188, using 2-hydroxymethyl-3-methoxypyridine, to give the title compound. MS (APCI+) *m/z* 158 $(M+H)^+$.

Preparation 194

2-Chloromethyl-6-methoxypyridine Hydrochloride

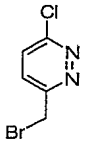


2-Hydroxymethyl-6-methoxypyridine: To 6-methoxy-pyridine-2-carbaldehyde (*J. Org. Chem.* 1990, *55*, 69-73) (11.0 g, 80.3 mmol) in wet THF (200 mL) add portion wise with stirring sodium borohydride (3.0 g, 79mmol) and continue stirring for 1 h at ambient temperature. Add brine, extract the reacton mixture twice with EtOAc, dry the organic layer over anhydrous Na_2SO_4 and concentrate *in vacuo*. Pass the residue through a small plug of silica gel eluting with hexane/EtOAc (3:1) to provide the desired intermediate as a clear liquid (9.0 g, 81%).

2-Chloromethyl-6-methoxypyridine hydrochloride: Use the chlorination method described in Preparation 187, using 2-hydroxymethyl-6-methoxypyridine, to give the title compound as a pale yellow solid. MS (APCI+) *m/z* 158 $(M+H)^+$.

Preparation 195

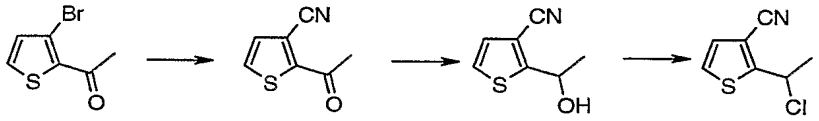
3-Bromomethyl-6-chloro-pyridazine



Use a method similar to the Preparation 184, using 3-chloro-6-methylpyridazine, to give the title compound as a red-orange liquid that darkens on standing.

Preparation 196

(±)-2-(1-Chloroethyl)-3-cyanothiophene



2-Acetyl-3-cyanothiophene: Heat a stirred solution of 2-acetyl-3-bromothiophene (1.49 g, 7.29 mmol) (*Chem. Pharm. Bull.* 2000, *48*, 1558-1566) in dry NMP (72 mL) for 10 h at 150 °C in the presence of copper cyanide (3.26 g, 36.5 mmol). Dilute the mixture with water, extract three times with diethyl ether, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give the desired intermediate as a dark oil (1.1 g, 99%).

(±)-2-(1-Hydroxyethyl)-3-cyanothiophene: Use a method similar to the reduction procedure described in Preparation 194, using 2-acetyl-3-cyanothiophene, to give the desired intermediate as dark oil.

(±)-2-(1-Chloroethyl)-3-cyanothiophene: Use a method similar to the Preparation 188, using (±)-2-(1-hydroxyethyl)-3-cyanothiophene, to give the title compound as dark oil. Use the crude material without further purification.

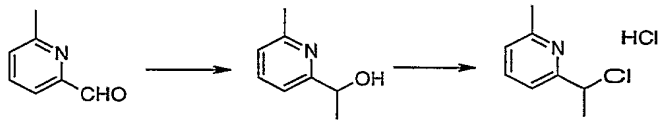
Preparation 197

(±)-2-(1-Bromoethyl)-pyridine

To (±)-2-(1-hydroxyethyl)-pyridine (*Bull. Chem. Soc. Jpn.* 1990, *63*, 461-465) (10.0 g, 81.3 mmol) in DCM (120 mL) at 0° C, add with stirring triphenylphosphine (22.39 g, 85.365 mmol) followed by NBS (15.2 g, 85.4 mmol) in portions. Warm the reaction mixture to ambient temperature and continue stirring for 3 h. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give the title compound.

Preparation 198

(±)-2-(1-Chloroethyl)-6-methylpyridine Hydrochloride

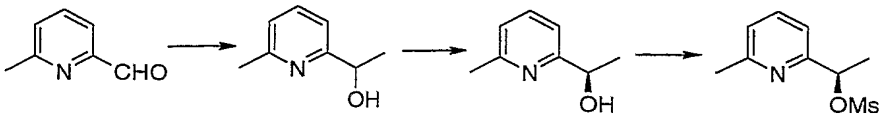


(±)-2-(1-Hydroxyethyl)-6-methylpyridine: To 6-methylpyridine-2-carboxaldehyde (2.0 g, 16.5 mmol) in dry THF (55 mL) at 0 °C under nitrogen, add a solution of 3M methyl magnesium bromide in ether (6.0 mL, 18.0 mmol,) dropwise with stirring. After 1 h at 0°C, quench with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the desired intermediate (crude, 2.3 g).

(±)-2-(1-Chloroethyl)-6-methylpyridine hydrochloride: To the crude 2-(1-hydroxyethyl)-6-methylpyridine (1.6 g, 11.7 mmol) in dry DCM (1 5 mL) add with stirring thionyl chloride (2.0 mL, 27 mmol) and continue stirring overnight. Concentrate *in vacuo*, azeotrope three times with dry chloroform and dry under high vacuum to provide the title compound as a tan solid (1.9 g, 85%). MS (APCI+) *m/z* 156 $(M+H)^+$.

Preparation 199

(*R*)-Methanesulfonic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester



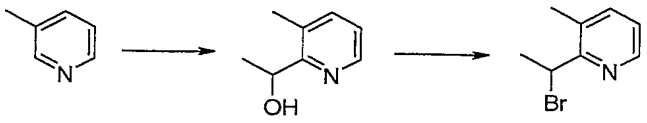
(±)-1-(6-Methyl-pyridin-2-yl)-ethanol: Use a method similar to the Preparation 198 (Step 1), using 6-methyl-2-pyridinecarboxaldehyde and methylmagnesium bromide, to give the desired intermediate.

(*R*)-1-(6-Methyl-pyridin-2-yl)-ethanol: Stir a mixture of 1-(6-methyl-pyridin-2-yl)-ethanol (2.9 g, 21 mmol), 4A molecular sieves powder (3 g), vinyl acetate (6 mL) and lipase Candida Antarctica acrylic resin (0.87 g) in *i*-Pr_2O (40 mL) at ambient temperature overnight (*J. Org. Chem.* 1998, *63*, 2481-2487; *Synlett* 1999, 41-44). Remove the solid residue by filtration. Evaporate the volatile substances and purify by chromatography eluting with hexane/EtOAc (7:3 to 1:1) to give the faster eluting (*R*)-acetic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester as colorless oil (1.9 g, 50%), and the slower eluting (*S*)-alcohol as light yellow oil (1.258 g, 43%). Dissolve (*R*)-acetic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester (1.72 g, 9.62 mmol) in methanol (50 mL) and add potassium carbonate (5.3 g, 38.5 mmol) in water (10 mL). Stir the mixture at ambient temperature for 4 h. Dilute with brine, extract three times with EtOAc, dry over anhydrous Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as a colorless oil (1.17 g, 89%).

(*R*)-Methanesulfonic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester: To a stirred solution of (*R*)-1-(6-methyl-pyridin-2-yl)-ethanol (175 mg, 1.28 mmol) and triethylamine (355 µl, 2.56 mmol) in DCM (5 mL) at 0°C add methanesulfonyl chloride (148 µl, 1.92 mmol). Stir at 0 °C for 30 min and quench the reaction mixture with saturated aqueous $NaHCO_3$ at the same temperature. Extract the mixture three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (8:2) to give the title compound as a colorless oil (274 mg, 100%).

Preparation 200

(±)-2-(1-Bromoethyl)-3-methyl-pyridine

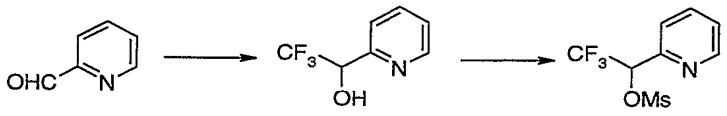


(±)-1-(3-Methyl-pyridin-2-yl)-ethanol: Dissolve *N,N*-dimethylethanolamine (70.45 mmol) in hexane (90 mL) at 0°C, add 2.5M *n*-butyl lithium in hexane (140.9 mmol,) and stir for 30 min at this temperature. Add a solution of 3-picoline (35.23 mmol) in hexane (10 mL) and continue stirring at 0° C for 1 h. Cool the resulting mixture to –78° C, add acetaldehyde (70.45 mmol) and continue stirring at –78° C for 1 h. Dilute with water, warm to ambient temperature, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography eluting with hexane/EtOAc (85:15) to give the desired intermediate as a light yellow oil.

(±)-2-(1-Bromoethyl)-3-methyl-pyridine: Use a method similar to the Preparation 197, using 1-(3-fluoro-pyridin-2-yl)-ethanol, to give the title compound.

Preparation 201

(±)-2-[1-Methanesulfonyloxy-(2,2,2-trifluoroethyl)]pyridine

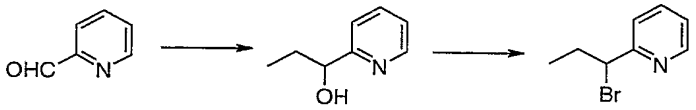


(±)-2-[1-Hydroxy-(2,2,2-trifluoroethyl)]-pyridine: To a stirred solution of 2-pyridine carboxaldehyde (2.09 g, 19.5 mmol) and (trifluoromethyl)trimethylsilane (3.33 g, 23.4 mmol) in THF (30 mL) at 0° C add 1M tetrabutylammonium fluoride in THF (956 µl, 0.956 mmol). Continue stirring for 30 min at 0° C and then at ambient temperature for 2 h. Add 1M aqueous HCl (20 mL) and stir 2 h at ambient temperature. Dilute with aqueous 1M aqueous NaOH to pH 8, extract the mixture three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography eluting with hexane/EtOAc (8:2) to give the desired intermediate as a yellow oil (3.22 g, 93%).

(±)-2-[1-Methanesulfonyloxy-(2,2,2-trifluoroethyl)]pyridine: Use a method similar to the Preparation 199 (Step 3), using (±)-2-[1-hydroxy-(2,2,2-trifluoroethyl)]pyridine, to give the title compound.

Preparation 202

(±)-2-(1-Bromopropyl)pyridine



(±)-1-Pyridin-2-yl-propan-1-ol: To a stirred solution of 2-pyridine carboxaldehyde (4.0 g, 37.34 mmol) in THF (50 mL) at 0° C, add 3M ethyl magnesium bromide in ether (18.7 mL, 56.0 mmol), continue stirring for 30 min at 0°C and then at ambient temperature for 2 h. Add water (200 mL), extract three times with EtOAc, dry over anhydrous Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as a yellow oil (3.39 g, 66%).

(±)-2-(1-Bromopropyl)pyridine: Use a method similar to the Preparation 197, using 1-pyridin-2-yl-propan-1-ol, to give the title compound.

Preparation 203

(±)-1-Pyridazin-3-yl-ethanol

3-(1-Ethoxyvinyl)pyridazine: Heat pyridazine-3-chloride (WO 0107416) (2 g, 17.5 mmol) with tributyl-(1-ethoxyvinyl)tin (7.1 mL, 21.1 mmol) and dichlorobis(triphenylphosphine)palladium(II) (1.1 g, 1.6 mmol) in DMF (18 mL) at 110°C for 13 h. Cool the mixture, dilute with ether (175 mL) and add a solution of potassium fluoride (5.43 g, 94 mmol) in water (10 mL). After 1 h, filter the mixture through Celite®, and wash the filtrate with brine. Dry the combined organic extracts over Na_2SO_4 and evaporate. Purify by chromatography on silica gel eluting with EtOAc:hexane (0:1 to 6:4) to obtain the desired intermediate (1.7 g, 65%). HPLC t_R=3.7

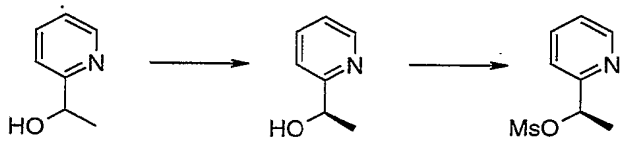
min (Zorbax Eclipse XBD-C8 4.6 x 150 mm 5 micron column, 1.5 mL/min of 90/10 to 10/90 0.1% TFA in water/acetonitrile over 10 min. Detector is at 230 and 254 nm.).

1-Pyridazin-3-yl-ethanone: Stir 3-(1-ethoxyvinyl)pyridazine (1.7 g, 11.3 mmol) in acetone (6.3 mL) and 2.5N aqueous HCl (3.1 mL) for 2 h at ambient temperature and evaporate. Dissolve the residue in DCM and wash the organic layer with saturated aqueous $NaHCO_3$, dry the organic layer over Na_2SO_4 and evaporate to obtain the desired intermediate (1.4 g, 99%). HPLC t_R=1.9 min (Zorbax Eclipse XBD-C8 4.6 x 150 mm 5 micron column, 1.5 mL/min of 90/10 to 10/90 0.1% TFA in water/acetonitrile over 10 min. Detector is at 230 and 254 nm.).

(±)-1-Pyridazin-3-yl-ethanol: To 1-pyridazin-3-yl-ethanone (1.4 g, 11.2 mmol) in methanol (112 mL) add sodium borohydride (0.85 g, 22.5 mmol) at 0 °C and stir for 1 h at ambient temperature. Evaporate the mixture and purify by chromatography on silica gel eluting with EtOAc:hexane (1:1 to 1:0) and methanol:EtOAc (0:1 to 1:9) to obtain the title compound (1.3 g, 93%).

Preparation 204

(*R*)-(-)-1-(2-Pyridinyl)ethanol methanesulfonate ester



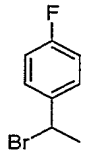
***(R)*-1-(Pyridin-2-yl)-ethanol:** Stir a mixture of (±)-1-(pyridin-2-yl)-ethanol (21.2 mmol), 4A molecular sieves powder (3 g), vinyl acetate (6 mL) and lipase Candida Antarctica acrylic resin (0.87 g) in *i*-Pr_2O (40 mL) at ambient temperature overnight (*J. Org. Chem.* 1998, *63*, 2481-2487; *Synlett* 1999, 41-44). Remove the solid residue by filtration. Evaporate the volatile substances and purify by chromatography eluting with hexane/EtOAc (7:3 to 1:1) to give the faster eluting (*R*)-acetic acid 1-(pyridin-2-yl)-ethyl ester as colorless oil (50%) and the slower eluting (*S*)-alcohol as light yellow oil (43%). Dissolve (*R*)-acetic acid 1-(pyridin-2-yl)-ethyl ester (9.620 mmol) in methanol (50 mL) and add potassium carbonate (38.48 mmol) in water (10 mL). Stir the mixture at ambient temperature for 4 h. Dilute with brine, extract three times with EtOAc, dry over

anhydrous Na_2SO_4, filter through a short pad of silica gel and concentrate *in vacuo* to give the desired intermediate as a colorless oil (89%).

(*R*)-(-)-1-(2-Pyridinyl)ethanol methanesulfonate ester: To a stirred solution of (*R*)-1-(pyridin-2-yl)-ethanol (1.28 mmol) and triethylamine (2.56 mmol) in DCM (5 mL) at 0°C add methanesulfonyl chloride (1.92 mmol). Stir at 0° C for 30 min and quench the reaction mixture with saturated aqueous $NaHCO_3$ at the same temperature. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the title compound as a colorless oil (100 %). MS (APCI+) *m/z* 202 $(M+H)^+$; $[\alpha]_D^{25} = -73.5°$ (c 1, $CHCl_3$).

Preparation 205

(±)-1-(4-Fluorophenyl)ethyl bromide



Method A: Add carbon tetrabromide (646 mg, 1.95 mmol) to a solution of triphenylphosphine (511 mg, 1.95 mmol) and (±)-4-fluoro-α-methylbenzyl alcohol (260 mg, 1.86 mol) in dry DMF (20 mL) at 0°C under nitrogen. Stir the reaction for 2 h to give the title compound. No further purification required.

Method B: Add HBr (460 µL of 48% w/w in water, 4.28 mmol) to a solution of (±)-4-fluoro-α-methylbenzyl alcohol (300 mg, 2.14 mmol) in dry DCM (10 mL) at ambient temperature under an atmosphere of nitrogen. Stir for 2.5 h. Reduce volume *in vacuo* to give the title compound. Dilute with DCM (1 mL) and use without further purification.

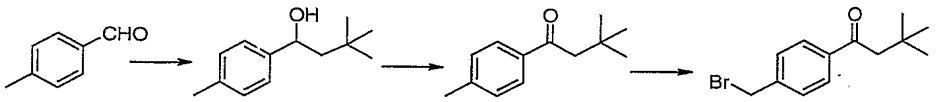
Preparation 206

(±)-2-(1-Bromoethyl)benzonitrile

Use a method similar to the Preparation 184, using 2-ethylbenzonitrile, to give the title compound as a clear liquid.

Preparation 207

1-(4-Bromomethylphenyl)-3,3-dimethylbutan-1-one



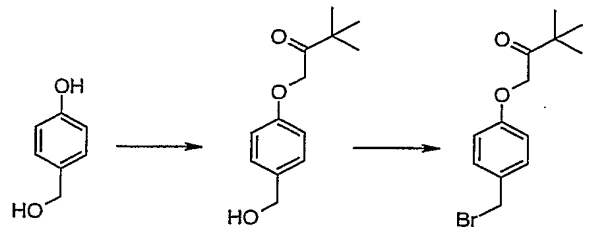
(±)-3,3-Dimethyl-1-p-tolylbutan-1-ol: To a stirred solution of 4-methylbenzaldehyde (1.51 g, 12.6 mmol) in THF (30 mL) at 0° C, add neopentyl magnesium chloride (33.0 mL, 16.34 mmol, 0.5-1M in ether) and continue stirring at 0 ° C for 1 h. Dilute with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (95:5) to give the desired intermediate as a colorless oil (2.15 g, 89%).

3,3-Dimethyl-1-*p*-tolyl-butan-1-one: To a stirred solution of (±)-3,3-dimethyl-1-*p*-tolyl-butan-1-ol (2.15 g, 11.3 mmol) in hexane (30 mL) add manganese dioxide (2.94 g, 33.8 mmol) and heat the mixture overnight at 65° C. Cool to ambient temperature, filter the manganese salts, and concentrate *in vacuo* to give the desired intermediate as a colorless oil (2.2 g, 100%).

1-(4-Bromomethylphenyl)-3,3-dimethylbutan-1-one: Use a method similar to the Preparation 184, using 3,3-dimethyl-1-*p*-tolylbutan-1-one, to give the title compound.

Preparation 208

1-(4-Bromomethylphenoxy)-3,3-dimethylbutan-2-one



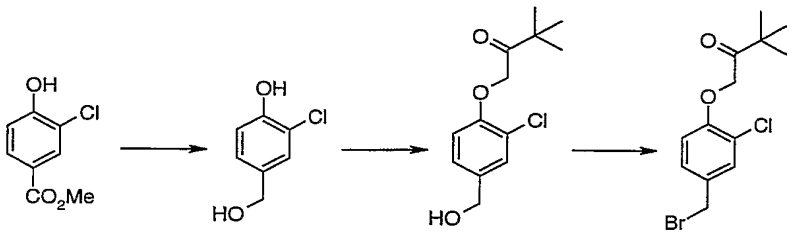
1-(4-Hydroxymethylphenoxy)-3,3-dimethylbutan-2-one: Mix potassium carbonate (2.764 g, 20 mmol), 4-hydroxy-benzyl alcohol (1.49 g, 12 mmol) in absolute ethanol (100

mL), add 1-bromopinacolone (1.791 g, 10 mmol) dropwise. Heat the mixture under reflux for 12 h. Add water to dissolve the solid, and remove most of the ethanol *in vacuo*. Extract the mixture with EtOAc three times. Combine the organic layers, wash with brine, dry over Na_2SO_4, filter and concentrate. Purify the residue by chromatography on silica gel eluting with EtOAc:hexane (1:2) to provide the desired intermediate as a colorless oil (1.08 g, 48%). MS (ES+) *m/z*: 205 $(M+H-H_2O)^+$.

1-(4-Bromomethylphenoxy)-3,3-dimethylbutan-2-one: Add phosphorous tribromide (1.45 g, 5.34 mmol) slowly to a solution of 1-(4-hydroxymethyl-phenoxy)-3,3-dimethylbutan-2-one (1.08 g, 4.85 mmol) in anhydrous THF under nitrogen at 0 °C. Stir at 0 °C for 1 h and then raise to ambient temperature. Stir overnight. Dilute with EtOAc, wash with saturated aqueous $NaHCO_3$, brine, dry over Na_2SO_4, filter and concentrate. Purify the residue by chromatography on silica gel eluting with EtOAc:hexane (1:6) to provide the title compound (1.152 g, 83%). MS (ES+) *m/z*: 205 $(M-Br)^+$.

Preparation 209

1-(4-Bromomethyl-3-chlorophenoxy)-3,3-dimethylbutan-2-one

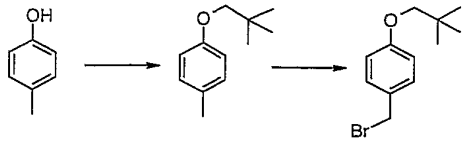


3-Chloro-4-hydroxybenzyl alcohol: Add a solution of DIBAL-H in toluene (1.0 M, 35 mL) to a solution of methyl 3-chloro-4-hydroxybenzoate (1.9 g, 10 mmol) at 0 °C under nitrogen. Stir the reaction at 0 °C and gradually warm to ambient temperature overnight. Quench the reaction with slow addition of 0.1N aqueous HCl, add more acid to break the gel-like solid to two clear layers. Separate the organic layer, and extract the aqueous layer with EtOAc three times. Combine the organic layers, wash with brine, dry over Na_2SO_4, filter and concentrate to give a white solid. MS (ES-) *m/z* 157 $(M-H)^-$.

1-(4-Bromomethyl-3-chlorophenoxy)-3,3-dimethyl-butan-2-one: Use a method similar to the Preparation 208 to convert 3-chloro-4-hydroxy-benzyl alcohol to the title compound (1.144 g, 64% two steps). MS (ES+) *m/z* 319.0 $(M+H)^+$.

Preparation 210

1-Bromomethyl-4-(2,2-dimethyl-propoxy)-benzene

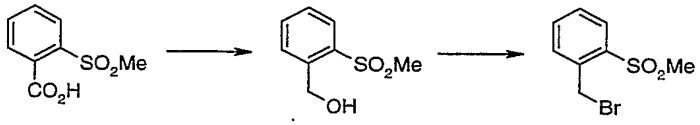


1-(2,2-Dimethyl-propoxy)-4-methyl-benzene: To a solution of *p*-cresol (526 mg, 4.87 mmol) in THF (50 mL), add with stirring diisopropyl azodicarboxylate (2.16 mL, 10.7 mmol) followed by triphenylphosphine (306 mg, 11.7 mmol) and neopentyl alcohol (5.15 g, 58.4 mmol). Heat at 60 °C for 3 h, cool to ambient temperature and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc to give the desired intermediate as a colorless oil.

1-Bromomethyl-4-(2,2-dimethyl-propoxy)-benzene: Use a method similar to the Preparation 184, using 1-(2,2-dimethyl-propoxy)-4-methylbenzene, to give the title compound.

Preparation 211

1-Bromomethyl-2-methanesulfonylbenzene

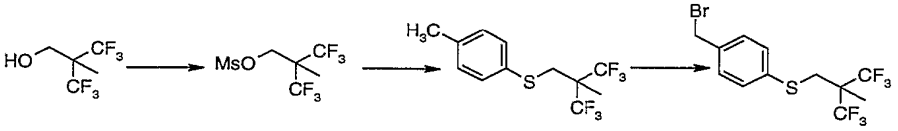


(2-Methanesulfonylphenyl)methanol: To a stirred solution of 2-methanesulfonyl-benzoic acid (2.7 g, 13.5 mmol) in dry THF (60 mL) at 0 °C, add a solution of borane in THF (27.0 mL, 0.5 M, 13.5 mmol). Allow the mixture to warm to ambient temperature and continue stirring for 2 days. Quench the excess borane by slow addition of methanol, add brine, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to provide the crude desired intermediate as a clear, thick oil (2.4 g, 97 %).

1-Bromomethyl-2-methanesulfonylbenzene: To a stirred solution of (2-methanesulfonyl-phenyl)methanol (735 mg, 3.99 mmol) in dry DCM (2 mL) at 0 °C, add a solution of 1M phosphorous tribromide in DCM (6.0 mL, 6.0 mmol) and continue stirring for 1 h. Dilute with saturated aqueous $NaHCO_3$, extract three times with ethyl ether, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (12:1) to provide the title compound as a white solid (950 mg, 97 %).

Preparation 212

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene



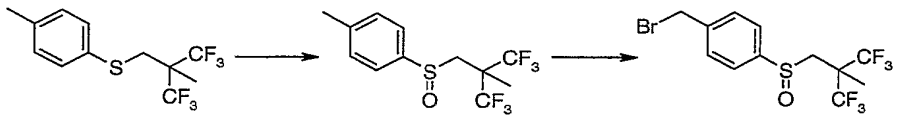
Methanesulfonic acid 3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propyl ester: To 2,2-bis(trifloromethyl)propanol (4.34 g, 22.1 mmol) in DCM (100 mL) at 0 °C add with stirring triethylamine (6.2 mL, 44 mmol) followed by methanesulfonyl chloride (2.6 mL, 33 mmol). After 15 min at 0 °C dilute with water and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the crude desired intermediate as a yellow oil (6.16 g, 100 %).

1-Methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene: In a sealed tube dissolve 4-methylbenzenethiol (4.13 g, 33.2 mmol) in DMF (20 mL) at ambient temperature. Add portionwise with stirring sodium hydride (899 mg, 37.5 mmol) followed by tetrabutylammonium iodide (82 mg, 0.22 mmol) and a solution of methanesulfonic acid 3,3,3-trifluoro-2-methyl-2-trifluoromethylpropyl ester (6.16 g, 22.5 mmol) in DMF (10 mL). Stir at 150 °C overnight, cool the mixture to ambient temperature and dilute cautiously with water. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane to give the desired intermediate as a yellow oil (4.5 g, 62 %).

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene: Use a method similar to the Preparation 184, using 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene, to give the title compound.

Preparation 213

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene

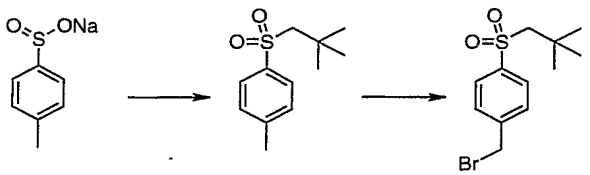


1-Methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene: To 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene (4.5 g, 14.9 mmol) in acetic acid (15 mL) at ambient temperature, add with stirring aqueous hydrogen peroxide (15 mL, 30% in water) and stir for 1 h. Dilute the reaction with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (4.125 g, 88 %).

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene: To 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzene (4.13 g, 13.0mmol) in carbon tetrachloride (50 mL) add NBS (2.31 g, 13.0 mmol), benzoyl peroxide (314 mg, 1.30 mmol) and stir overnight at reflux. Cool to ambient temperature, dilute with water and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the title compound as colorless oil (2.3 g, 55 %).

Preparation 214

1-Bromomethyl-4-(2,2-dimethylpropane-1-sulfonyl)benzene

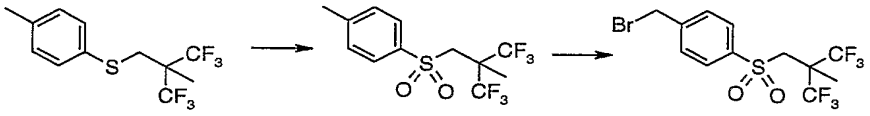


1-(2,2-Dimethyl-propane-1-sulfonyl)-4-methyl-benzene: In a sealed tube, dissolve *p*-toluenesulfinic acid sodium salt (5.71 g, 32.1 mmol) in DMF (20 mL) and water (10 mL). Add *neo*-pentyl bromide (6.3 mL, 48 mmol) and tetrabutylammonium iodide (592 mg, 1.60 mmol) and heat the mixture at 145 °C overnight. Cool the reaction to ambient temperature, dilute with water and extract 3 times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (3.3 g, 45 %).

1-Bromomethyl-4-(2,2-dimethylpropane-1-sulfonyl)benzene: Use a method similar to the Preparation 213 (Step 2), using 1-(2,2-dimethylpropane-1-sulfonyl)-4-methyl-benzene, to give the title compound.

Preparation 215

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)-benzene

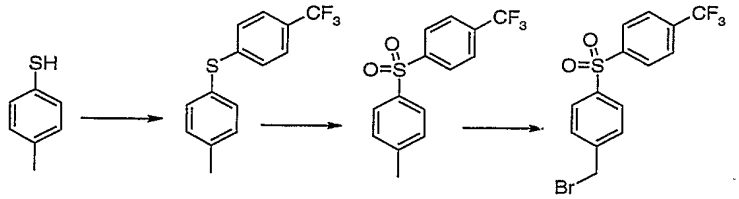


1-Methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)benzene: To 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)benzene (3.47 g, 11.49 mmol) in trifluoroacetic acid (15 mL) at ambient temperature add with stirring aqueous hydrogen peroxide (15 mL, 30% in water) and stir for 1 h. After removing trifluoroacetic acid *in vacuo*, dilute with saturated aqueous $NaHCO_3$. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a colorless oil (2.8 g, 74 %).

1-Bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)-benzene: Use a method similar to the Preparation 213 (Step 2), using 1-methyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)benzene, to give the title compound.

Preparation 216

1-Bromomethyl-4-(4'-trifluoromethyl)-phenylsulfonylbenzene

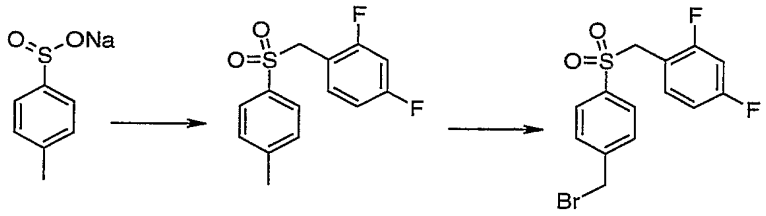


1-Methyl-4-(4-trifluoromethyl)-phenylthio-benzene: Heat a mixture of 4-methylbenzenethiol (7.67 g, 61.8 mmol), 1-bromo-4-trifluoromethyl-benzene (4.63 g, 20.6 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (379 mg, 2.06 mmol), cesium carbonate (20.1 g, 61.8 mmol) and CuCl (102 mg, 1.03 mmol) in NMP (30 mL) at 150° C for 3 h. Cool the mixture to ambient temperature, dilute with water, extract three times with EtOAc, dry the organic layer over anhydrous Na_2SO_4, and concentrate *in vacuo*. Recrystallize the residue from hexane/EtOAc to give the desired intermediate as a white solid (3.87 g, 70%).

1-Bromomethyl-4-(4-trifluoromethyl)-phenylsulfonyl-benzene: Use a method similar to the Preparation 215, using 1-methyl-4-(4-trifluoromethyl)-phenylthiobenzene, to give the title compound.

Preparation 217

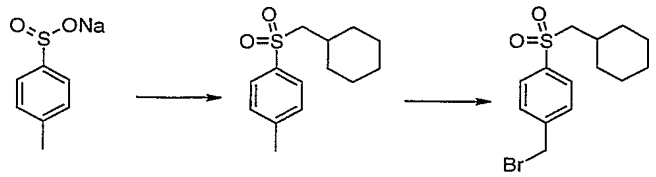
1-(4-Bromomethylbenzenesulfonylmethyl)-2,4-difluorobenzene



Use a method similar to the Preparation 214, using 2,4-difluorobenzyl bromide, to give the title compound.

Preparation 218

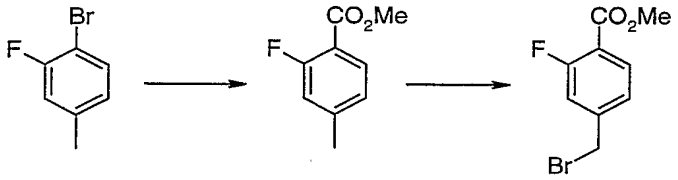
1-Bromomethyl-4-cyclohexylmethanesulfonyl-benzene



Use a method similar to the Preparation 214, using cyclohexylmethyl bromide, to give the title compound.

Preparation 219

Methyl 4-bromomethyl-2-fluorobenzoate

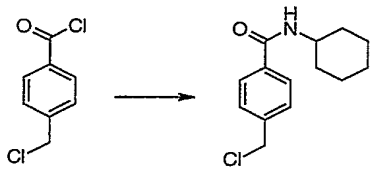


Methyl 2-fluoro-4-methyl-benzoate: Mix 1-bromo-2-fluoro-4-methylbenzene (15 g, 79.4 mmol), palladium acetate (712 mg, 3.17 mmol), 1,3-bis(diphenylphosphino)-propane (2.94 g, 7.14 mmol), triethylamine (16.1 g, 159 mmol) in methanol (150 mL) and DMF (100 mL). Degas the mixture under vacuo and pressurize to 65 psi with carbon monoxide. Stir the reaction at 110 °C for 2 days. Remove methanol *in vacuo*, dilute the mixture with water, and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give the desired intermediate as a white solid (7.40 g, 55%).

Methyl 4-bromomethyl-2-fluoro-benzoate: Use a method similar to the Preparation 184, using methyl 2-fluoro-4-methylbenzoate, to give the title compound as a white solid.

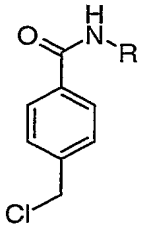
Preparation 220

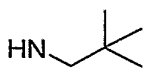
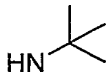
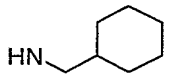
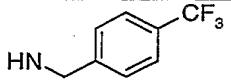
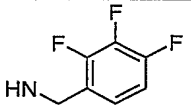
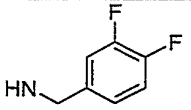
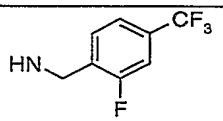
4-Chloromethyl-*N*-cyclohexylbenzamide

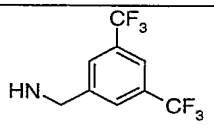
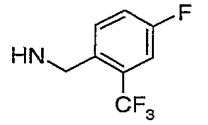
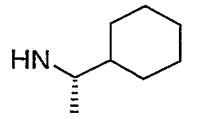
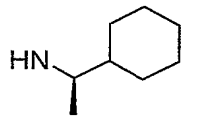
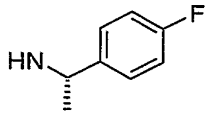
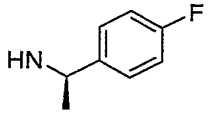
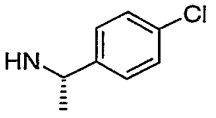
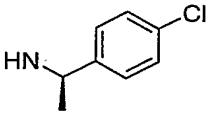


To 4-chloromethylbenzoyl chloride (1.03 g, 5.47 mmol) in DCM (20 mL) at 0 °C, add with stirring triethylamine (0.839 mL, 6.02 mmol) followed by cyclohexylamine (0.688 mL, 6.02 mmol), and continue stirring for 15 min. Dilute the reaction mixture with aqueous 1M hydrochloric acid, extract three times with EtOAc, wash with water and saturated aqueous $NaHCO_3$. Dry the combined organic extracts over anhydrous Na_2SO_4 and concentrate *in vacuo* to give the title compound as a white solid (1.31 g, 95%).

The compounds of Preparations 221-235 may be prepared essentially as described in Preparation 220by using 4-chloromethylbenzoyl chloride and the appropriate amine.

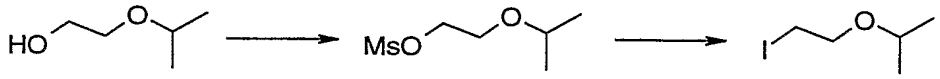


Prep.	NH-R	Compound
221		4-Chloromethyl-*N*-(2,2-dimethyl-propyl)-benzamide
222		*N-tert*-Butyl-4-chloromethyl-benzamide
223		4-Chloromethyl-*N*-cyclohexylmethyl-benzamide
224		4-Chloromethyl-*N*-(4-trifluoromethyl-benzyl)-benzamide
225		4-Chloromethyl-*N*-(2,3,4-trifluoro-benzyl)-benzamide
226		4-Chloromethyl-*N*-(3,4-difluoro-benzyl)-benzamide
227		4-Chloromethyl-*N*-(2-fluoro-4-trifluoromethyl-benzyl)-benzamide

Prep.	NH-R	Compound
228		*N*-(3,5-Bis-trifluoromethyl-benzyl)-4-chloromethyl-benzamide
229		4-Chloromethyl-*N*-(4-fluoro-2-trifluoromethyl-benzyl)-benzamide
230		(*S*)-4-Chloromethyl-*N*-(1-cyclohexyl-ethyl)-benzamide
231		(*R*)-4-Chloromethyl-*N*-(1-cyclohexyl-ethyl)-benzamide
232		(*S*)-4-Chloromethyl-*N*-[1-(4-fluoro-phenyl)-ethyl]-benzamide
233		(*R*)-4-Chloromethyl-*N*-[1-(4-fluoro-phenyl)-ethyl]-benzamide
234		(*S*)-4-Chloromethyl-*N*-[1-(4-chloro-phenyl)-ethyl]-benzamide
235		(*R*)-4-Chloromethyl-*N*-[1-(4-chlorophenyl)-ethyl]-benzamide

Preparation 236

2-(2-Iodoethoxy)propane



Methanesulfonic acid 2-isopropoxyethyl ester: To a stirred solution of 2-isopropoxyethanol (2.0 mL, 17.37 mmol) in DCM (100 mL) at ambient temperature add methanesulfonyl chloride (1.48 mL, 18.08 mmol). Add triethylamine (2.70 mL, 19.37 mmol) slowly followed by DMAP (catalytic). Continue stirring overnight and concentrate *in vacuo*. Add diethyl ether and filter. Wash the filtrate with aqueous 1N

aqueous HCl, brine, and saturated aqueous $NaHCO_3$. Dry over anhydrous $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate (2.97 g, 94%).

2-(2-Iodoethoxy)propane: To a stirred solution of methanesulfonic acid 2-isopropoxy-ethyl ester (2.95 g, 16.2 mmol) in acetone (200 mL) at ambient temperature add sodium iodide (7.28 g, 19.4 mmol) and continue stirring overnight. Concentrate *in vacuo,* add diethyl ether and filter, and concentrate *in vacuo* to give the title compound as a pale yellow liquid (3.12 g, 90%).

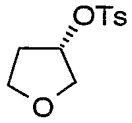
Preparation 237

(*R*)-Toluene-4-sulfonic Acid Tetrahydrofuran-3-yl Ester

To (*R*)-tetrahydro-furan-3-ol (2.0 g, 22.7 mmol), triethylamine (3.8 mL, 27.3 mmol), DMAP (277 mg, 2.26 mmol), and silver oxide (5.26 g, 22.7 mmol) in dry DCM (30 mL) at 0 °C under nitrogen, add portion wise with stirring *p*-toluenesulfonyl chloride (4.76 g, 25.0 mmol). Warm to ambient temperature overnight, filter from silver salts, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:1) to give the title compound as a clear liquid (4.7 g, 85%).

Preparation 238

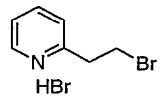
(*S*)-Toluene-4-sulfonic Acid Tetrahydrofuran-3-yl Ester



Use a method similar to the Preparation 237, using (*S*)-tetrahydro-furan-3-ol, to give the title compound as a clear liquid.

Preparation 239

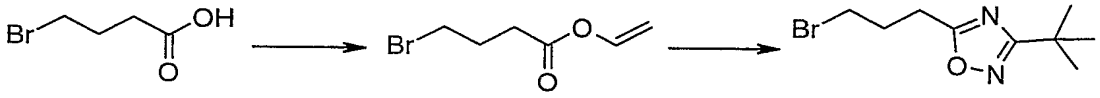
2-(2-Bromoethyl)-pyridine Hydrobromide



Use a method similar to the bromination procedure described in Preparation 186 (Step 2), using 2-pyridineethanol, to give the title compound. Recrystallize from 2-propanol to give a light brown solid.

Preparation 240

5-(3-Bromopropyl)-3-*tert*-butyl-[1,2,4]oxadiazole

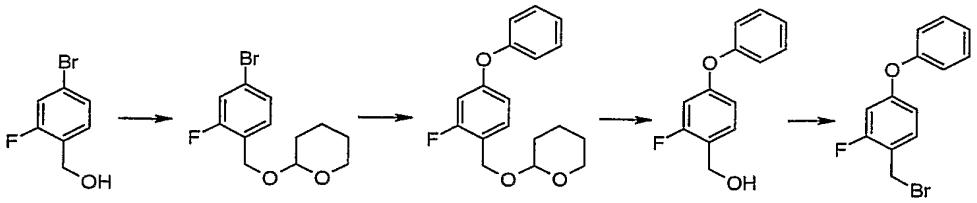


4-Bromobutyric acid vinyl ester: To 4-bromobutyric acid (1.0 g, 6.0 mmol) in vinyl acetate (54 mL) add with stirring palladium(II) acetate (188 mg, 0.84 mmol) and continue stirring overnight at ambient temperature. Filter and concentrate *in vacuo* to provide the crude desired intermediate.

5-(3-Bromopropyl)-3-*tert*-butyl-[1,2,4]oxadiazole: Use a method similar to the Preparation 178, using 4-bromobutyric acid vinyl ester, to give the title compound.

Preparation 241

1-Bromomethyl-2-fluoro-4-phenoxybenzene



2-(4-Bromo-2-fluoro-benzyloxy)-tetrahydro-pyran: Mix under nitrogen atmosphere 4-bromo-2-fluorobenzyl alcohol, (4.1 g, 20 mmol), dihydropyran (2 g, 24 mmol), *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol), and anhydrous DCM (70 mL). Stir for 16 h at ambient temperature. Dilute with DCM, wash sequentially with saturated aqueous $NaHCO_3$ then brine. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc

(1:0 and 9:1) to obtain the desired intermediate as a clear oil (4.36 g, 75%). MS (ES+) *m/z*: 312 $(M+Na)^+$.

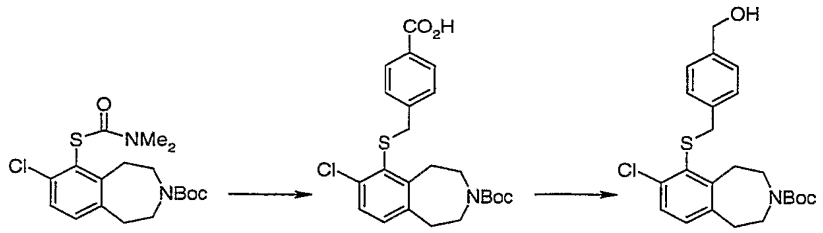
2-(2-Fluoro-4-phenoxy-benzyloxy)-tetrahydro-pyran: Mix under argon atmosphere 2-(4-bromo-2-fluorobenzyloxy)-tetrahydropyran (2.9 g, 10 mmol), phenol (1.9 g, 20 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (184.3 mg, 1.0 mmol), cesium carbonate (6.5 g, 20 mmol) and anhydrous NMP (20 mL). Degas the flask and fill with argon. Add copper(I) chloride (495 mg, 5 mmol) quickly. Degas the flask three times then fill with argon. Heat at 120 °C for 3 h. Cool to ambient temperature. Dilute with EtOAc and filter. Concentrate *in vacuo* and purify by chromatography on silica gel to obtain the desired intermediate (2.05 g, 68%). MS (ES+) *m/z*: 325 $(M+Na)^+$.

(2-Fluoro-4-phenoxy-phenyl)-methanol: Mix under nitrogen atmosphere 2-(2-fluoro-4-phenoxy-benzyloxy)-tetrahydro-pyran (2.05g, 6.8 mmol), methanol (60 mL) and *p*-toluenesulfonic acid monohydrate (260 mg, 1.35 mmol). Stir at ambient temperature for 16 h. Dilute with EtOAc. Wash with saturated aqueous $NaHCO_3$. Separate the organic layer, dry over Na_2SO_4 and concentrate *in vacuo* to give the desired intermediate (1.41 g, 95%). MS (ES+) *m/z*: 201 $(M-OH)^+$.

1-Bromomethyl-2-fluoro-4-phenoxy-benzene: Dissolve under nitrogen atmosphere (2-fluoro-4-phenoxyphenyl)-methanol (1.41 g, 6.5 mmol) in anhydrous THF (60 mL). Cool to 0 °C in an ice bath. Add phosphorous tribromide (2.11 g, 7.8 mmol). Stir at cold for 1 h, then remove the ice bath and stir at ambient temperature for 16 h. Quench the reaction with saturated aqueous $NaHCO_3$. Extract aqueous phase three times with EtOAc. Combine organic fractions, wash with brine, dry over Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1). Evaporate the solvent to obtain the title compound (1.31 g, 72%).

Preparation 242

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

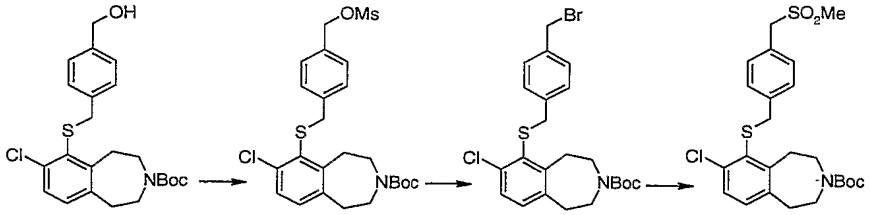


3-*tert*-Butoxycarbonyl-6-(4-carboxy-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 2.6 mmol) in methanol (15 mL) under nitrogen, add with stirring potassium hydroxide (4.5 g, 80.3 mmol) at ambient temperature. Heat at 55-60°C for 2 h, cool to ambient temperature, and add methyl 4-bromomethylbenzoate (1.2 g, 5.2 mmol). TLC after 20 min shows formation of product; however, after 4 h at ambient temperature both TLC and LC/MS indicate complete hydrolysis of the ester and the carbamate. Dilute with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude material in THF (10 mL), treat with di-*tert*-butyl-dicarbonate (2 equiv) and saturated aqueous $NaHCO_3$ (10 mL), and stir overnight. Extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as an oil that was used without purification [2.32 g, 50% purity with $(Boc)_2O$]. MS (ES+) *m/z* 348 $(M+H\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-6-(4-carboxybenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.85 g, 50% purity, 2.06 mmol) in anhydrous THF (40 mL) under nitrogen, add with stirring 1M borane in THF (4.2 mL) at 0 °C. Warm to ambient temperature and stir 2-3 h. Quench by the careful addition of water (3 mL), dilute with saturated aqueous $NaHCO_3$, extract three times with ethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to provide the title compound as a white solid (485 mg, 54 %).

Preparation 243

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-methanesulfonylmethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



3-*tert*-Butoxycarbonyl-7-chloro-6-(4-methanesulfonyloxymethyl -benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (170 mg, 0.391 mmol) in anhydrous DCM under nitrogen, add methanesulfonyl chloride (33 μL, 0.426 mmol) and triethylamine (61 μL, 0.44 mmol) and continue stirring for 2 h. Dilute with water (5 mL) and extract three times with DCM. Wash the combined organic extracts with brine, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to obtain the desired intermediate that was used without purification.

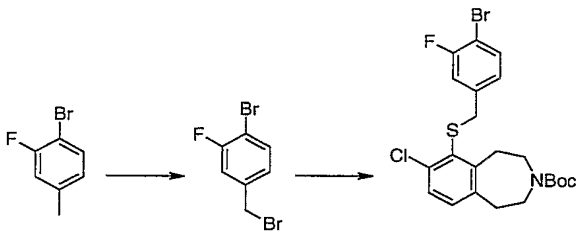
3-*tert*-Butoxycarbonyl-6-(4-bromomethyl -benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-(4-methanesulfonyloxymethyl -benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous acetone (3 mL), treat with anhydrous lithium bromide (335 mg, 3.89 mmol) and continue stirring overnight. Add water, extract the reaction mixture three times with ethyl ether, wash with brine, dry over anhydrous $MgSO_4$, and concentrate *in vacuo* to obtain the desired intermediate that was used without purification.

3-*tert*-Butoxycarbonyl-7-chloro-6-(4-methanesulfonylmethyl -benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To the crude 3-*tert*-butoxycarbonyl-6-(4-bromomethyl -benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous DMF (1 mL) under nitrogen, add with stirring sodium methanesulfinate (400 mg, 3.9 mmol), and continue stirring for 30 min at ambient temperature followed by 2 h at 40 °C. Add water, extract three times with EtOAc, wash with brine, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with

hexane/EtOAc (3:1) to give a clear oil that solidifies on standing to a white solid (118 mg, 61%).

Preparation 244

6-(4-Bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine

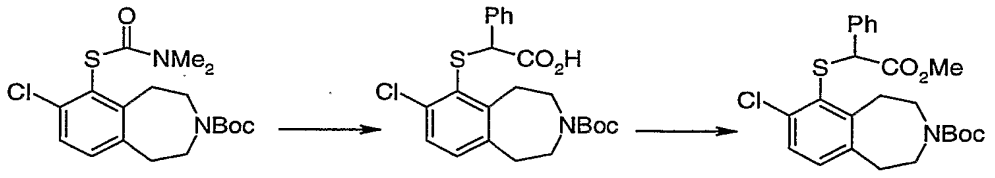


1-Bromo-4-bromomethyl-2-fluorobenzene: Use a method similar to the Preparation 184, using 4-bromo-3-fluorotoluene, to give the desired intermediate as a white solid.

6-(4-Bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromo-4-bromomethyl-2-fluorobenzene, to give the title compound as a white solid.

Preparation 245

(±)-3-*tert*-Butoxycarbonyl-7-chloro-6-(1-methoxycarbonyl-1-phenyl-methyllthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



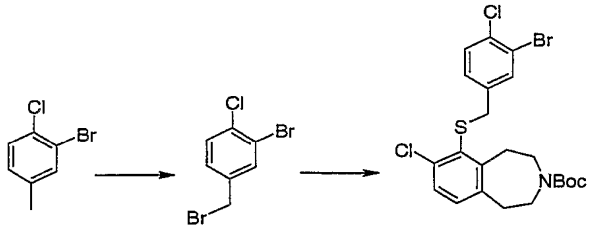
(±)-3-*tert*-Butoxycarbonyl-6-(1-carboxy-1-phenyl-methyllthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.23 g, 3.2 mmol) in methanol (20 mL) under nitrogen, add with stirring potassium hydroxide (5.36 g, 95.5 mmol) at ambient temperature. Heat at 55-60 °C for 2 h, cool to ambient temperature,

and add methyl α-bromophenylacetate (600 μL, 3.81 mmol). After 30 min, dilute with saturated aqueous NH_4Cl, extract three times with EtOAc, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude material in THF (10 mL), treat with di-*tert*-butyl-dicarbonate (2 equiv) and saturated aqueous $NaHCO_3$ (10 mL), and stir overnight. Extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo* to give the desired intermediate as an oil that is used without purification (1.1 g, 77%).

(±)-3-*tert*-Butoxycarbonyl-6-(1-methoxycarbonyl-1-phenyl-methyllthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Treat a solution of 3-*tert*-butoxycarbonyl-6-(1-carboxy-1-phenyl-methylthio)-7-chloro-2,3,4,5-tetrahydrobenzo[*d*]azepine (200 mg, 0.447 mmol) in anhydrous DMF (2 mL) with methyl iodide (317 mg, 2.237 mmol) and potassium carbonate (310 mg, 2.237 mmol) for 1.5 h at ambient temperature. Add water and extract the aqueous phase three times with EtOAc. Dry the organic phase over $MgSO_4$ and concentrate to obtain the title compound that was used without purification.

Preparation 246

6-(3-Bromo-4-chloro-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

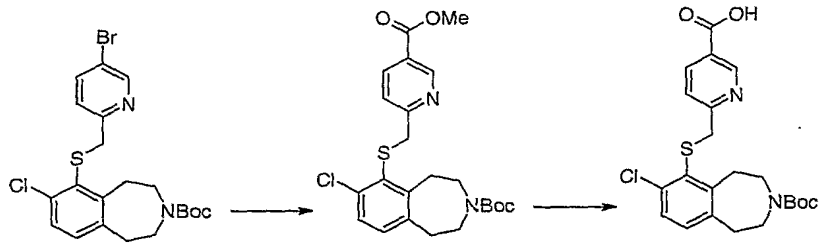


2-Bromo-4-bromomethyl-1-chloro-benzene: Use a method similar to the Preparation 184, using 3-bromo-4-chlorotoluene, to give the desired intermediate.

6-(3-Bromo-4-chloro-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylsulfanyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromo-4-bromomethyl-1-chloro-benzene, to give the title compound.

Preparation 247

3-*tert*-Butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

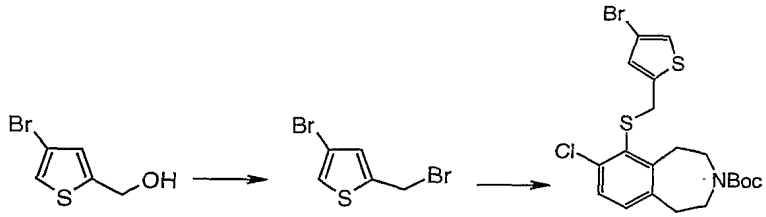


3-*tert*-Butoxycarbonyl-7-chloro-6-(5-methoxycarbonyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 3-*tert*-butoxycarbonyl-6-(5-bromopyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.13 g, 4.40 mmol), palladium acetate (35 mg, 0.156 mmol), 1,1'-bis(diphenylphosphino)ferrocene (150 mg, 0.271 mmol) and triethylamine (1.30 mL) in methanol (10 mL) and DMF (5 mL). Degas and then heat under a balloon filled with carbon monoxide at 75 ° C for 10 h. Remove methanol *in vacuo*, and dilute the mixture with water. Extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (7:1) to give the desired intermediate as a clear oil (1.86 g, 91%). MS (APCI+) *m/z* 463 $(M+H)^+$, 363 $(M+H\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(5-methoxycarbonyl-pyridin-2-ylmethylthio)-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.86 g, 4.03 mmol) in methanol (25 mL). Add 1M aqueous lithium hydroxide (12 mL) and stir at ambient temperature overnight. Remove methanol *in vacuo*, and dilute the mixture with cold 0.5M aqueous HCl to pH 4. Add brine and extract three times with EtOAc. Dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give the title compound as an off-white solid (1.78 g, 95%). MS (APCI+) *m/z* 449 $(M+H)^+$, 349 $(M+H\text{-}Boc)^+$.

Preparation 248

6-(4-Bromo-thiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine

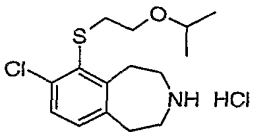


3-Bromo-5-bromomethyl-thiophene: Use the bromination procedure described in Preparation 211 (Step 2), using (3-bromothiophen-2-yl)methanol (*Synthesis* 1983, *1*, 73-75), to give the desired intermediate as a light brown liquid.

6-(4-Bromo-thiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-bromo-5-bromomethyl-thiophene, to give the title compound as a gum.

Example 315

7-Chloro-6-(2-isopropoxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

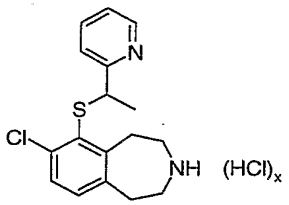


To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.52 mmol) in methanol (5 mL) under nitrogen, add potassium hydroxide (0.9 g, 16.1 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60 °C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature, add aqueous saturated ammonium chloride, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude 3-*tert*-butoxycarbonyl-

7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous THF (5 mL) under nitrogen and add with stirring 1.0 M potassium *t*-butoxide in THF (1.0 mL) at ambient temperature. After 10 min, add 2-(2-iodoethoxy)propane (223 mg, 1.04 mmol), and allow the reaction to continue overnight. Dilute with aqueous saturated ammonium chloride, extract the mixture three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (12:1) to provide 3-*tert*-butoxycarbonyl-7-chloro-6-(2-isopropoxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (127 mg, 63 %). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 316

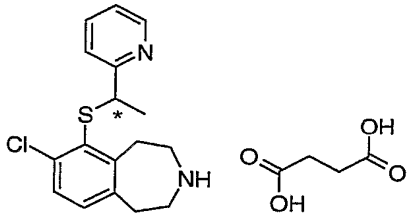
(±)-7-Chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-bromoethyl)-pyridine to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 319 $(M+H)^+$.

Example 317

(-)-7-Chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

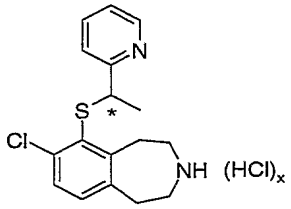


Separate the enantiomers of (±)-7-chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralpak AD 8x30 cm column, eluting with 0.2% DMEA in methanol). Take the second eluting isomer and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (100:1 to 80:20).

Use the General Procedure 2-1 to give the title compound as a white solid (4.27 g, 33%). MS (ES+) *m/z*: 319 $(M+H)^+$; ee = 99.4%; $[\alpha]^{20}_D$ -179° (c 0.5, CH_3OH).

Example 318

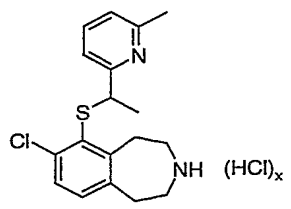
(-)-7-Chloro-6-(1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 7, except that the alkylation is conducted at 0° C, to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (*R*)-(-)-1-(2-pyridinyl)ethanol methanesulfonate ester. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (APCI+) *m/z*: 319 $(M+H)^+$; ee = 98.6% [Chiral HPLC: Chiralpak AD-H 0.46x15 cm column, eluting with 15:85 ethanol/heptane].

Example 319

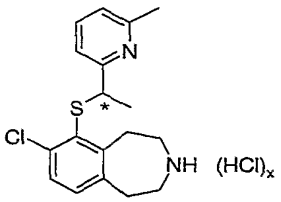
(±)-7-Chloro-6-[1-(6-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 315, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-chloroethyl)-6-methylpyridine hydrochloride to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a tan solid. MS (ES+) *m/z*: 333 $(M+H)^+$.

Example 320

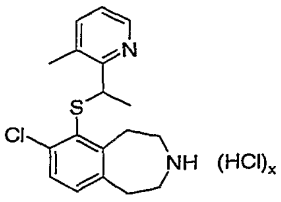
7-Chloro-6-[1-(6-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride, Isomer 1



Use a method similar to the Preparation 177, except that the alkylation is conducted at 0° C, to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (*R*)-methanesulfonic acid 1-(6-methyl-pyridin-2-yl)-ethyl ester. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 333 $(M+H)^+$; ee >97%, t_R = 6.53 min. (Chiral HPLC: Chiralpak OJ 120Å 4.6x250 mm, 45 °C; eluent: 20% isopropanol with 0.05% triethylamine in SFC, flow rate 2 mL/min, UV detector at 234 nm).

Example 321

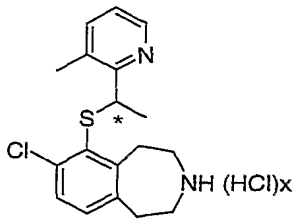
(±)-7-Chloro-6-[1-(3-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (±)-2-(1-bromoethyl)-3-methyl-pyridine. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 333 $(M+H)^+$.

Example 322

(-)-7-Chloro-6-[1-(3-methylpyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

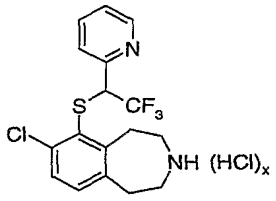


Separate the enantiomers of (±)-7-chloro-[1-(3-methyl-pyridin-2-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralpak AD 8x30 cm column, eluting with 85:15 heptane:0.2% DMEA in ethanol). Take the second eluting isomer and purify by SCX column chromatography.

Use the General Procedure 2-2 to give the title compound as a white solid (60 mg, 43%). MS (ES+) *m/z*: 333 $(M+H)^+$; $[\alpha]^{20}_D$ -232° (c 0.5, CH_3OH).

Example 323

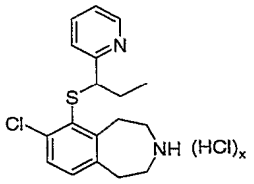
(±)-7-Chloro-6-(2,2,2-trifluoro-1-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (±)-2-[1-methanesulfonyloxy-(2,2,2-trifluoroethyl)]-pyridine. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 373 $(M+H)^+$.

Example 324

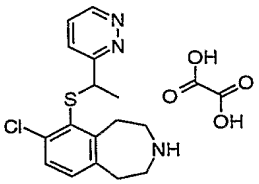
(±)-7-Chloro-6-(1-pyridin-2-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with (±)-2-(1-bromopropyl)pyridine. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 333 $(M+H)^+$.

Example 325

(±)-7-Chloro-6-[1-(pyridazin-3-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

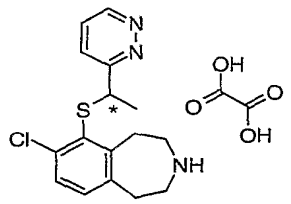


Dissolve (±)-1-pyridazin-3-yl-ethanol (38 mg, 0.31 mmol) in thionyl chloride (0.14 mL) at 0°C and stir for 1 h at ambient temperature. Evaporate the mixture, add toluene and evaporate again. Treat this residue with the thiolate prepared from 7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ether (0.1 g, 0.25 mmol) according to the General Procedure 7 in the presence of potassium carbonate (0.3 g, 2.25 mmol) in DMF (3 mL) at 80°C for 16 h.

Use a method similar to the General Procedure 1-5, basic work-up, and a method similar to the General Procedure 2-5 to give the title compound (38 mg, 37%). HRMS calcd for $C_{16}H_{19}ClN_3S$ 320.0988, found 320.0970.

Example 326

(+)-7-Chloro-6-[1-(pyridazin-3-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Oxalate

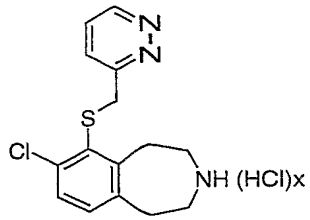


Dissolve (±)-1-pyridazin-3-yl-ethanol (0.29 g, 2.35 mmol) in thionyl chloride (1.0 mL) at 0°C and stir for 1 h at ambient temperature. Evaporate the mixture, add toluene and evaporate again. Treat this residue with the thiolate prepared from 7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ether (0.72 g, 1.88 mmol) according to the General Procedure 7 in the presence of potassium carbonate (2.60 g, 18.8 mmol) and tetrabutylammonium iodide (7 mg, 0.02 mmol) in DMF (20 mL) at 80 °C for 28 h. Separate the enantiomers by preparative HPLC (Waters Symmetry C18 4.6 x 150 mm 3.5 micron column, 1 mL/min of 90:10 to 50:50:0.1% TFA in water:ACN over 25 min. Detector is at 254 nm) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(pyridazin-3-yl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, isomer 1.

Use a method similar to the General Procedure 1-5, basic work-up, and a method similar to the General Procedure 2-5 to give the title compound (56 mg, 7%). HPLC t_R = 3.0 min (Chiralpak AD-H 4.6x150 mm, 3 micron column, 1.0 mL/min of 99.8:0.2 methanol/dimethyethylamine isocratic; detector at 225 nm); HRMS calc'd for $C_{16}H_{19}ClN_3S$ 320.0988, found 320.1001. $[\alpha]^{20}_D$ +160° (c 0.5, CH_3OH).

Example 327

7-Chloro-6-(pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

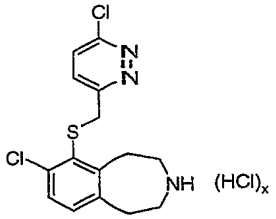


React 3-chloromethyl-pyridazine (prepared as described in WO 99/54333, WO 98/49166) (1.8 g, 11.0 mmol) with 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.2 g, 5.7 mmol) according to the General Procedure 7 in the presence of tetrabutylammonium iodide (0.1 g, 0.27 mmol) at ambient temperature for 3 h.

Use a method similar to the General Procedure 1-4 to give the title compound as a tan powder (1.9 g, 98 %): HRMS calcd for $C_{15}H_{16}ClN_3S$ 306.0832, found 306.0829.

Example 328

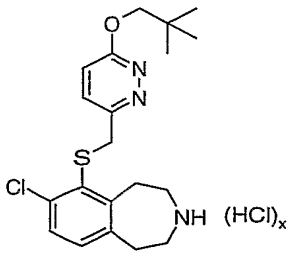
7-Chloro-6-(6-chloro-pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-bromomethyl-6-chloropyridazine to give 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the General Procedure 1-4 to give the title compound as an off-white powder. MS (APCI+) *m/z*: 340 $(M+H)^+$.

Example 329

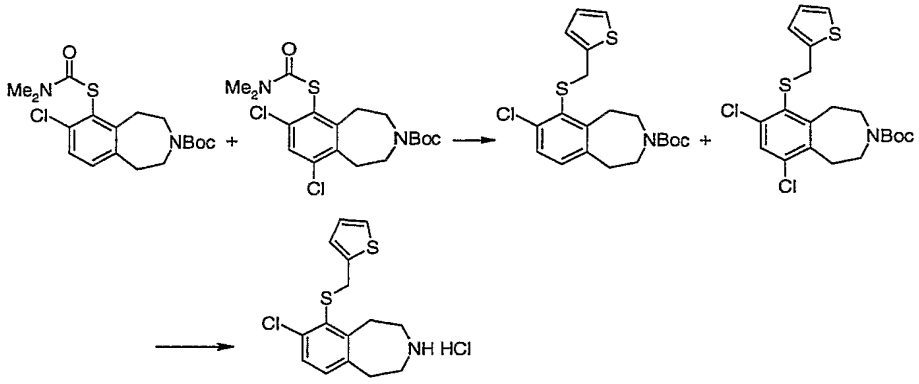
7-Chloro-6-[6-(2,2-dimethylpropoxy)-pyridazin-3-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of neopentyl alcohol (105 mg, 1.19 mmol) in THF (5 mL) at ambient temperature add sodium hydride (31 mg, 95%, 1.19 mmol) and continue stirring for 3 h at ambient temperature. Add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloro-pyridazin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (315 mg, 0.59 mmol) in THF (1 mL) and continue stirring overnight at ambient temperature and then at 60°C for 1 h. Dilute with water, extract the reaction mixture three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (6:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[6-(2,2-dimethyl-propoxy)-pyridazin-3-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (81 mg, 28%). MS (APCI+) *m/z*: 492 $(M+H)^+$, 392 $(M+H\text{-}Boc)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white powder. MS (APCI+) *m/z*: 392 $(M+H)^+$, *m/z*: 322 $(M+H\text{-}C_5H_{11})^+$.

Example 330

7-Chloro-6-(thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride

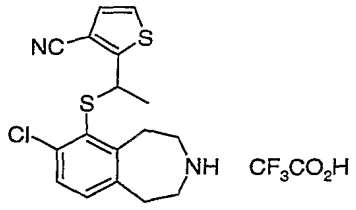


To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine (108 mg, 0.281 mmol) in methanol (3 ml), add potassium hydroxide pellets (504 mg, 9.0 mmol) and heat the mixture 2 h at 50 °C. Cool the reaction to ambient temperature, add 2-chloromethylthiophene (186 μL, 1.406 mmol), and continue stirring for 30 min. Dilute with EtOAc and water. Separate the layers and extract the aqueous layer three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (19:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-benzo[*d*]azepine as a colorless oil (36 mg, 31%).

Use a method similar to the General Procedure 1-5, using 3-*tert*-butoxycarbonyl-7-chloro-6-(thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-benzo[*d*]azepine to give, after basic workup and a method similar to the General Procedure 2-2, the title compound as a white solid. MS (ES+) *m/z*: 310 $(M+H)^+$.

Example 331

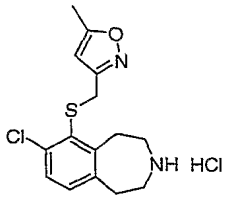
(±)-7-Chloro-6-(3-cyanothiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-chloroethyl)-3-cyanothiophene to give, after deprotection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (APCI+) *m/z*: 349 $(M+H)^+$.

Example 332

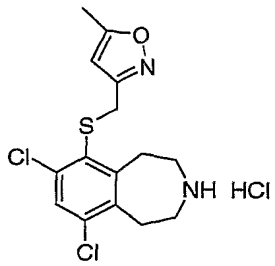
7-Chloro-6-(5-methylisoxazol-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.521 mmol) in methanol (3.3 mL) under nitrogen add potassium hydroxide (0.9 g, 16.1 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60°C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature, add 3-(chloromethyl)-5-methylisoxazole (82 mg, 0.62 mmol) and continue stirring for 30 min. Add aqueous saturated ammonium chloride, extract the mixture three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Treat a solution of the crude material so obtained in DCM (2 mL) with 2M hydrogen chloride in ether (excess) and continue stirring until TLC shows consumption of the starting material. Concentrate *in vacuo,* purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol, and convert to the hydrochloride by following a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 309 $(M+H)^+$.

Example 333

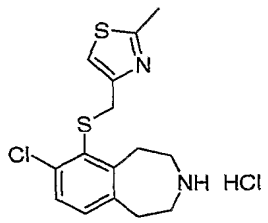
7,9-Dichloro-6-(5-methylisoxazol-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 332, after preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 343 $(M+H)^+$.

Example 334

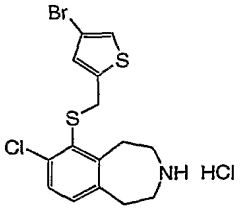
7-Chloro-6-(2-methylthiazol-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 332, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-chloromethyl-2-methylthiazole hydrochloride to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 325 $(M+H)^+$.

Example 335

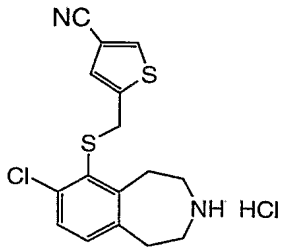
6-(4-Bromothiophen-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using 6-(4-bromothiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (APCI+) *m/z*: 390 $(M+H)^+$.

Example 336

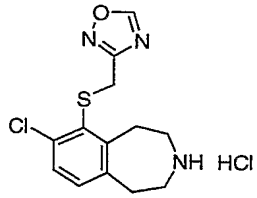
7-Chloro-6-(4-cyanothiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Degas a stirred solution of 6-(4-bromothiophen-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (183 mg, 0.37 mmol), zinc cyanide (50 mg, 0.42 mmol) and tetrakistriphenylphosphine palladium(0) (30 mg, 0.026 mmol) in dry DMF. Purge with dry nitrogen, and heat at 120°C for 6 h. Dilute with water, extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyanothiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (85 mg, 52%). MS (APCI+) *m/z*: 335 $(M+H\text{-}Boc)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (APCI+) *m/z*: 335 $(M+H)^+$.

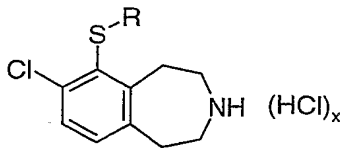
Example 337

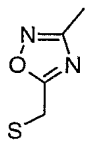
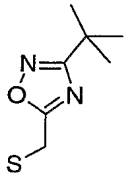
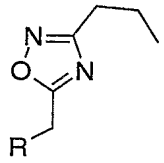
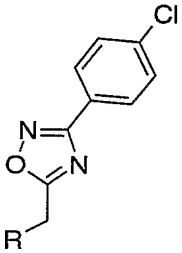
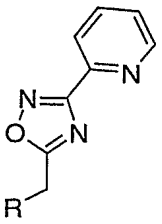
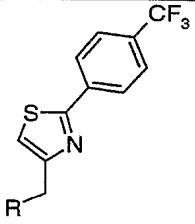
7-Chloro-6-([1,2,4]-oxadiazol-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-chloromethyl-1,2,4-oxadiazole to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z* 296 $(M+H)^+$.

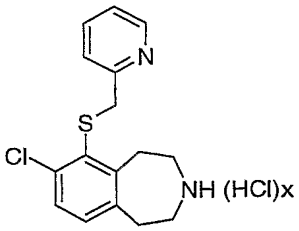
Examples 338-343 may be prepared essentially as described in Example 337 using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted 5-chloromethyl-1,2,4-oxadiazole or 4-chloromethyl-thiazole. MS (ES+) data are included in the Table below.



Ex.	SR	Compound	MS (ES+) *m/z*
338		7-Chloro-6-(3-methyl-[1,2,4]oxadiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	310 $(M+H)^+$
339		6-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	352 $(M+H)^+$
Ex.	**SR**	**Compound**	**MS (ES+) *m/z***
340		7-Chloro-6-(3-propyl-[1,2,4]oxadiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	338 $(M+H)^+$
341		7-Chloro-6-[3-(4-chloro-phenyl)-[1,2,4]oxadiazol-5-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	406 $(M+H)^+$
342		7-Chloro-6-(3-pyridin-2-yl-[1,2,4]oxadiazol-5-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	373 $(M+H)^+$
343		7-Chloro-6-[2-(4-trifluoromethylphenyl)-thiazol-4-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	455 $(M+H)^+$

Example 344

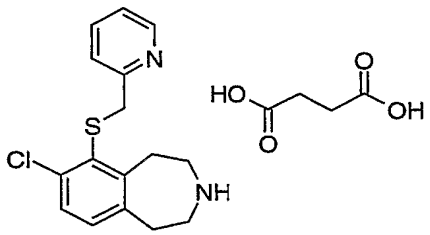
7-Chloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Using a method similar to the General Procedure 7, react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylaminocarbonylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (8 g, 20.8 mmol) with 2-picolyl chloride hydrochloride (3.41 g, 20.8 mmol). Dilute the reaction mixture with diethyl ether and filter the precipitate. Concentrate the filtrate *in vacuo*, dissolve the residue in diethyl ether (100 mL) and add 1N aqueous HCl (100 mL). Stir the mixture for 16 h at ambient temperature. Separate, wash the aqueous layer with diethyl ether, adjust the pH of the aqueous layer to 12 with sodium hydroxide and extract with diethyl ether. Dry over Na_2SO_4 and concentrate *in vacuo* to give the free base of the title compound. Use the General Procedure 2-2 to give the title compound as a white solid (4.91 g, 78%). MS (ES+) *m/z*: 305 $(M+H)^+$.

Example 345

7-Chloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

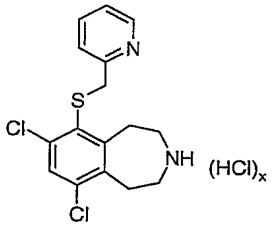


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1 equiv.) in methanol (0.1-0.4 M) and add potassium hydroxide (8-20 equiv.). Stir at 60°C for 4-24 h. Cool the reaction mixture in an ice bath, add picolyl chloride hydrochloride (1-3 equiv.) and stir the mixture at ambient temperature for 16-24 h. Add a volume of toluene approximately equal to the volume of

the reaction mixture and concentrate the resulting mixture to approximately ½ the resulting total volume and repeat this process once more. Add water until all solids dissolve and separate the layers. Dry the organic layer over Na_2SO_4 and filter. Heat the solution (containing about 0.25-0.40 M of free base of the title compound) to 50-75°C and then optionally seed with previously formed crystals of the title compound. Add succinic acid (1-1.3 equivalents) in isopropyl alcohol (0.25-0.40M solution) to the solution over 5-45 min. Cool the solution to 20-25°C over 1-3 h and filter, rinsing with a solution of toluene/isopropyl alcohol (1:1). Dry the resulting solid under vacuum at 50-70°C/5 Torr to give the title compound as a white solid, mp 159-160 °C. Anal. Calc'd for $C_{20}H_{23}ClN_2O_4S$: C, 56.80; H, 5.48; N, 6.62. Found: C, 56.56; H, 5.41; N, 6.57.

Example 346

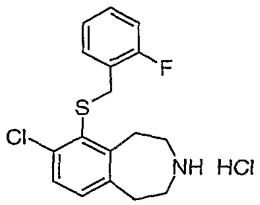
7,9-Dichloro-6-(pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 2-bromomethylpyridine hydrobromide, using a method similar to the General Procedure 7. Treat a solution of the crude mixture in DCM with 4M hydrogen chloride in dioxane (excess) overnight. Concentrate *in vacuo* and purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to give the title compound as an off-white solid. MS (APCI+) *m/z*: 339 $(M+H)^+$.

Example 347

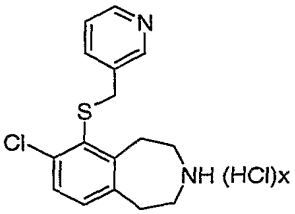
7-Chloro-6-(2-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine (102 mg, 0.267 mmol) in methanol (2 ml), add potassium hydroxide pellets (450 mg, 8.02 mmol) and heat the mixture 3 h at 60 °C. Cool to ambient temperature, add aqueous saturated ammonium chloride solution, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Dissolve the crude thiophenol thus obtained in dry DCM (2 mL) under nitrogen, and add DBU (80 □L, 0.54 mmol) and 2-fluorobenzyl bromide (65 □L, 0.54 mmol) with stirring. Stir overnight at ambient temperature, dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (31 mg, 25%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 322 $(M+H)^+$.

Example 348

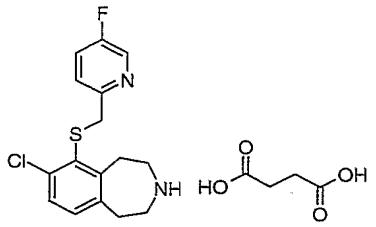
7-Chloro-6-(pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-(bromomethyl)pyridine hydrobromide to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 305 $(M+H)^+$.

Example 349

7-Chloro-6-(5-fluoropyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

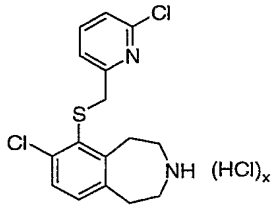


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (527 mg, 1.4 mmol) and potassium hydroxide (1.1 g, 20.5 mmol) in methanol (10 mL) and heat the solution to reflux for 2 h. Cool the reaction mixture to ambient temperature and remove the solvent *in vacuo*. Slurry the residue with EtOAc (50 ml), and wash the slurry with a saturated NH_4Cl. Collect and dry the organic phase over Na_2SO_4, remove the solvent under reduced pressure to obtain the intermediate thiophenol as an oil. Dissolve the oil in DMSO (10 ml), add triethylamine (1.1 ml, 8.2 mmol) and methanesulfonic acid 5-fluoro-pyridin-2-ylmethyl ester (500mg, 2.4 mmol). Heat the reaction mixture to 60 °C for 1 h. Monitor the reaction by HPLC and TLC. Cool the reaction to ambient temperature, add 1:1 hexane/EtOAc (80 ml) and wash the organic layer with a 5% NaCl (3 X 30 ml). Collect the organic layer, concentrate, and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1 to 1:1) to obtain 3-*tert*-butoxycarbonyl-7-chloro-6-(5-fluoro-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (519 mg, 89%). MS (ES+) *m/z*: 423 $(M+H)^+$.

Use the General Procedure 1-4 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-(5-fluoro-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (510 mg, 1.2 mmol). Purify by SCX chromatography followed by chromatography on silica gel eluting with DCM/2M ammonia in methanol (99:1 to 90:10). Use the General Procedure 2-1 to give the title compound (370 mg, 70%). MS (ES+) *m/z*: 323 $(M+H)^+$.

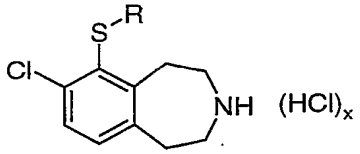
Example 350

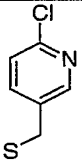
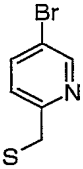
7-Chloro-6-(6-chloropyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

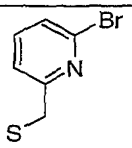
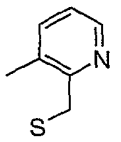
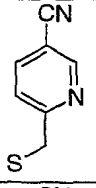
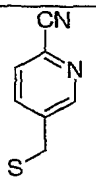
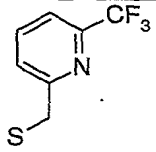
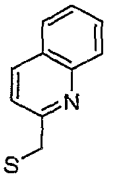


Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromomethyl-6-chloropyridine hydrochloride to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 339 $(M+H)^+$.

Examples 351-360 may be prepared essentially as described in Example 350 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted chloromethylpyridine, bromomethylpyridine or chloromethylquinoline. MS (ES+) data are included in the Table below.

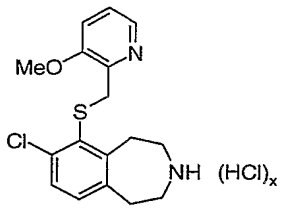


Ex.	SR	Compound	MS (ES+ or APCI+)
351		7-Chloro-6-(6-chloro-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	339 $(M+H)^+$
352		6-(5-Bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	385 $(M+H)^+$

Ex.	SR	Compound	MS (ES+ or APCI+)
353		6-(3-Bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	385 $(M+H)^+$
354		6-(6-Bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	385 $(M+H)^+$
355		7-Chloro-6-(3-methyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	319 $(M+H)^+$
356		7-Chloro-6-(5-cyano-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	330 $(M+H)^+$
357		7-Chloro-6-(6-cyano-pyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	330 $(M+H)^+$
358		7-Chloro-6-(6-trifluoromethyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	373 $(M+H)^+$
359		7-Chloro-6-(3-trifluoromethyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	373 $(M+H)^+$
360		7-Chloro-6-(quinolin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	355 $(M+H)^+$

Example 361

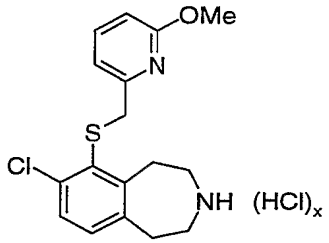
7-Chloro-6-(3-methoxypyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 315, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloromethyl-3-methoxypyridine to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid (71 mg). MS (APCI+) *m/z*: 335 $(M+H)^+$.

Example 362

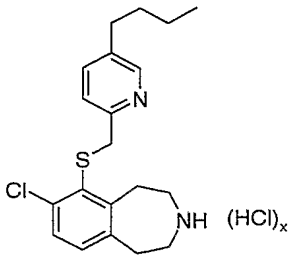
7-Chloro-6-(6-methoxypyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloromethyl-6-methoxypyridine hydrochloride to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid (120 mg). MS (APCI+) *m/z*: 335 $(M+H)^+$.

Example 363

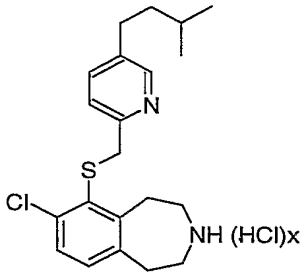
6-(5-Butylpyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 315, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-butyl-2-chloromethylpyridine hydrochloride to give the title compound as a white solid. MS (APCI$^+$) *m/z*: 330 $(M+H)^+$.

Example 364

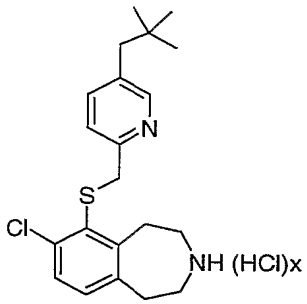
7-Chloro-6-[5-(3-methylbutyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To 6-(5-bromo-pyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (219 mg, 0.452 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (18 mg, 0.022 mmol) under dry nitrogen add with stirring a solution of 0.5M 3-methylbutylzinc bromide in THF (4.6 mL, 2.3 mmol). Degas, purge with dry nitrogen, and stir overnight at ambient temperature. Dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(3-methyl-butyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (160 mg, 75%). MS (APCI+) *m/z*: 475 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a tan solid. MS (APCI+) *m/z*: 375 $(M+H)^+$.

Example 365

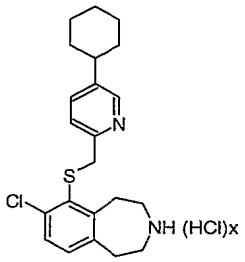
7-Chloro-6-[5-(2,2-dimethylpropyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of 1.0 M neopentyl magnesium chloride in diethyl ether (50 mL, 50 mmol) at –78 °C under nitrogen, add via syringe a solution of 0.5 M zinc chloride in THF (100 mL, 50 mmol). Warm gradually to ambient temperature and transfer via syringe of this solution (25 mL, ~8.33 mmol) to a stirred solution of 3-*tert*-butoxycarbonyl-6-(5-bromo-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.62 mmol) in THF (2 mL) at ambient temperature. Add dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (50 mg, 0.061 mmol) and heat at 65°C for 6 h. Cool to ambient temperature, dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography onr silica gel eluting with hexane/EtOAc (6:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(2,2-dimethyl-propyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (69 mg, 24%). MS (APCI+) *m/z*: 501 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white powder. MS (APCI+) *m/z*: 375 $(M+H)^+$.

Example 366

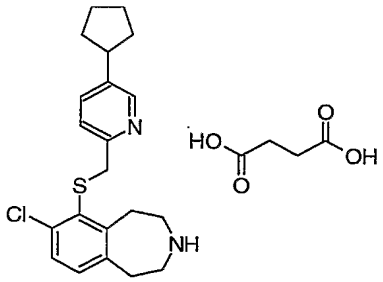
7-Chloro-6-(5-cyclohexylpyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a mixture of 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (146 mg, 0.30 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (12 mg, 0.015 mmol) under dry nitrogen add with stirring a solution of 0.5 M cyclohexylzinc bromide in THF (3.0 mL, 1.5 mmol). Degas, purge with dry nitrogen, and stir overnight at 60 °C. Cool to ambient temperature, dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (5:1) to give 3-tert-butoxycarbonyl-7-chloro-6-(5-cyclohexyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (46 mg, 32%). MS (APCI+) *m/z*: 487 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (APCI+) *m/z*: 387 $(M+H)^+$.

Example 367

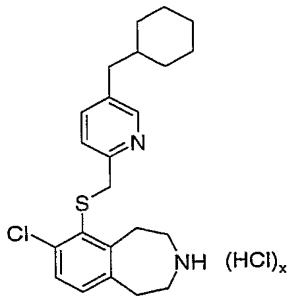
7-Chloro-6-(5-cyclopentylpyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 366 to react 6-(5-bromo-pyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with a solution of cyclopentylzinc bromide in THF. Use a method similar to the General Procedure 1-4, basic workup, and a method similar to the General Procedure 2-1 to give the title compound as a tan solid. MS (APCI+) *m/z*: 373 $(M+H)^+$.

Example 368

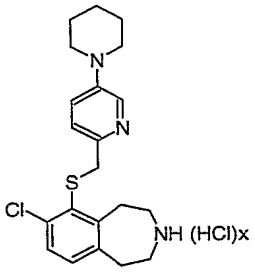
7-Chloro-6-(5-cyclohexylmethylpyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 366 to react 6-(5-bromo-pyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with cyclohexylmethylzinc bromide. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 401 $(M+H)^+$.

Example 369

7-Chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



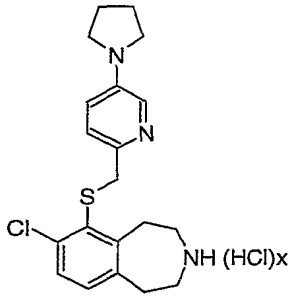
In a sealed tube, add tris(dibenzylideneacetone)dipalladium(0) (3.44 mg, 0.00376 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (4.98 mg, 0.00752 mmol) to a mixture of 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (242 mg, 0.501 mmol), sodium *tert*-butoxide (96 mg, 1.0 mmol), 18-crown-6 (13 mg, 0.050 mmol) and piperidine (496 μL, 5.01 mmol) in toluene (3 mL). Flush the mixture with nitrogen and heat overnight. Cool to ambient temperature, dilute with water and extract three times with EtOAc. Dry over anhydrous

Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (179 mg, 73%).

Use a method similar to the General Procedure 1-5, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,3']bipyridinyl-6'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after basic workup and a method similar to the General Procedure 2-2, the title compound as a yellow solid. MS (ES+) *m/z*: 388 $(M+H)^+$.

Example 370

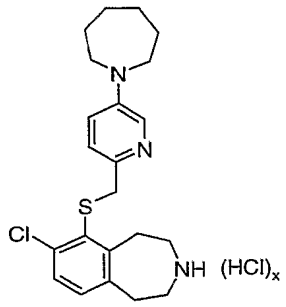
7-Chloro-6-(5-pyrrolidin-1-yl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 369, using 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyrrolidine to give the title compound as a pale yellow solid. MS (ES+) *m/z*: 374 $(M+H)^+$.

Example 371

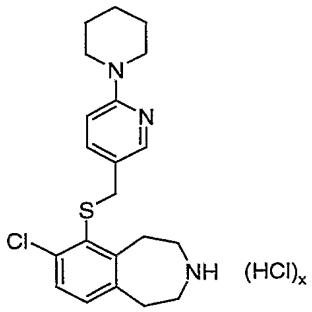
6-(5-Azepan-1-yl-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 369, using 6-(5-bromopyridin-2-ylmethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and homopiperidine to give the title compound as a yellow solid. MS (ES+) *m/z* 402 $(M+H)^+$.

Example 372

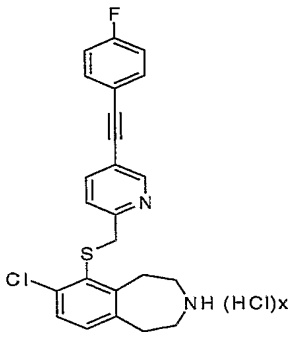
7-Chloro-6-(3,4,5,6-tetrahydro-2*H*-[1,2']bipyridinyl-5'-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 369, using 3-*tert*-butoxycarbonyl-7-chloro-6-(6-chloropyridin-3-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and piperidine, to give the title compound as a white solid. MS (ES+) *m/z*: 388 $(M+H)^+$.

Example 373

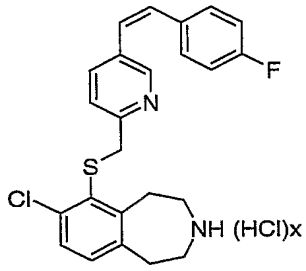
7-Chloro-6-[5-(4-fluorophenylethynyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Dissolve 3-*tert*-butoxycarbonyl-6-(5-bromopyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 2.07 mmol), tetrakistriphenylphosphine palladium(0) (120 mg, 0.104 mmol), cuprous iodide (20 mg, 0.105 mmol), triethylamine (2.60 mL) and 1-ethynyl-4-fluorobenzene (500 mg, 4.16 mmol) in DMF (8 mL). Degas the mixture, purge with nitrogen, and heat at 65 ° C for 3 days. Dilute the mixture with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (50:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(4-fluorophenylethynyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a tan foam (1.02 g, 95%). MS (APCI+) *m/z*: 523 $(M+H)^+$, 423 $(M+H\text{-}Boc)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a tan powder. MS (APCI+) *m/z*: 423 $(M+H)^+$.

Example 374

(*Z*)-7-Chloro-6-{5-[2-(4-fluorophenyl)vinyl]-pyridin-2-ylmethylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

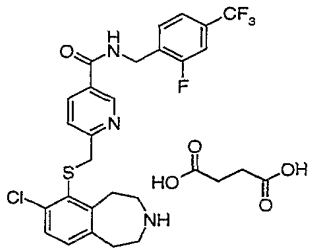


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(4-fluorophenylethynyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 1.9 mmol), Lindlar catalyst (240 mg), and quinoline (0.8 mL) in methanol (30 mL). Degas, purge with nitrogen, and stir under a balloon of hydrogen for 36 h. Filter the mixture and wash the catalyst with

additional methanol. Concentrate the filtrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (8:1) to give (*Z*)-3-*tert*-butoxycarbonyl-7-chloro-6-{5-[2-(4-fluoro-phenyl)-vinyl]-pyridin-2-ylmethylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil (630 mg, 63%). MS (APCI+) *m/z*: 525 $(M+H)^+$, 425 $(M+H\text{-}Boc)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a pale yellow solid. MS (APCI+) *m/z*: 425 $(M+H)^+$.

Example 375

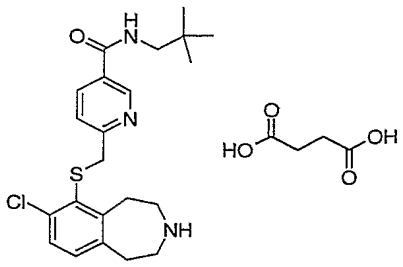
7-Chloro-6-[5-(2-fluoro-4-trifluoromethylbenzylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Dissolve 3-*tert*-butoxycarbonyl-6-(5-carboxypyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (300 mg, 0.67 mmol) in DMF (5.0 mL). Treat successively with HATU (305 mg, 0.802 mmol), *N,N*-diisopropylethylamine (140 µL, 0.804 mmol) and 2-fluoro-4-(trifluoromethyl)benzylamine (260 mg, 1.34 mmol). Stir overnight at 40° C. Dilute the mixture with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (3:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[5-(2-fluoro-4-trifluoromethyl-benzylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a foam (409 g, 98%). Use a method similar to the General Procedure 1-4 to give, after basic work-up and a method similar to the General Procedure 2-1, the title compound as an off-white solid. MS (APCI+) *m/z*: 524 $(M+H)^+$.

Example 376

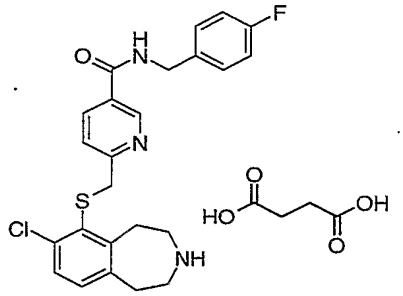
7-Chloro-6-[5-(2,2-dimethylpropylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine Succinate



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and neopentylamine, to give the title compound as an off-white solid. MS (APCI+) *m/z*: 418 $(M+H)^+$.

Example 377

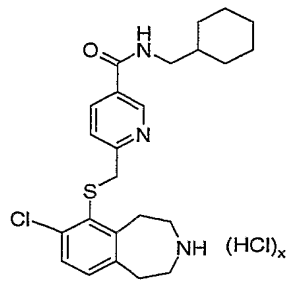
7-Chloro-6-[5-(4-fluoro-benzylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-fluorobenzylamine, to give the title compound as an off-white solid. MS (APCI+) *m/z*: 456 $(M+H)^+$.

Example 378

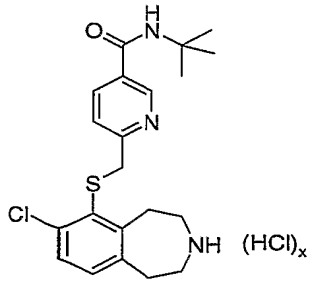
7-Chloro-6-[5-(cyclohexylmethylcarbamoyl)-pyridin-2-ylmethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and aminomethylcyclohexane to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 444 $(M+H)^+$.

Example 379

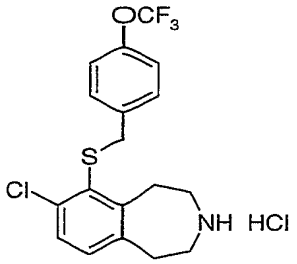
6-(5-*tert*-Butylcarbamoyl-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 375, using 3-*tert*-butoxycarbonyl-6-(5-carboxy-pyridin-2-ylmethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and *tert*-butylamine to give, after deprotection by the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 404 $(M+H)^+$.

Example 380

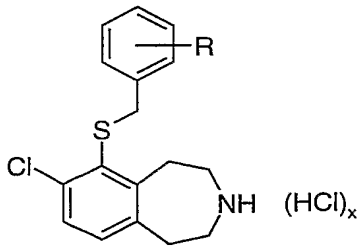
7-Chloro-6-(4-trifluoromethoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (102 mg, 0.27 mmol) in methanol (1.7 mL) under nitrogen, add potassium hydroxide (0.9 g, 16.1 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60 °C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature, add aqueous saturated ammonium chloride solution, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous DCM (2 mL) under nitrogen. Add with stirring DBU (80 μL, 0.532 mmol) and 4-(trifluoromethoxy)benzyl bromide (77 μL, 0.53 mmol) at ambient temperature and allow the reaction to continue overnight. Dilute with aqueous saturated ammonium chloride solution, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Treat a solution of the crude 3-*tert*-butoxycarbonyl-7-chloro-6-(4-trifluoromethoxy-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in DCM (2 mL) with 2M hydrogen chloride in ether (excess) and continue stirring until TLC shows consumption of starting material. Concentrate *in vacuo* and triturate the obtained solid with ether/pentane (10:90). Purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol and convert to the hydrochloride by following a method similar to the General Procedure 2-2 to give the title compound as a white solid (48 mg, 43%). MS (APCI+) *m/z*: 388 $(M+H)^+$.

Examples 381-383 may be prepared essentially as described in Example 380 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl bromide. Example 382 may be purified after deprotection by preparative reverse phase HPLC [Column: YMC ODS-AQ

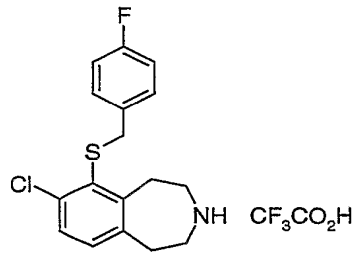
120Å 20x250mm [S10-20μm], eluent: gradient from 95:5 to 5:95 A/B, flow rate: 15 mL/min; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol]. MS (ES+) data are included in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
381	2-Cl	7-Chloro-6-(2-chloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	338 $(M+H)^+$
382	2-CN	7-Chloro-6-(2-cyano-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	329 $(M+H)^+$
383	4-Ph	7-Chloro-6-(4-phenyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	380 $(M+H)^+$

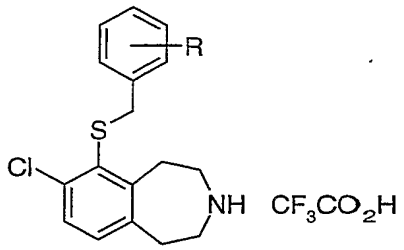
Example 384

7-Chloro-6-(4-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 380 to react 3-*tert*-butoxylcarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine with 4-fluorobenzyl bromide. Purify by preparative reverse phase HPLC [Column: YMC ODS-AQ 120Å 20 x 250mm [S10-20μm], eluent: gradient from 95:5 to 5:95 A/B, flow rate: 15 mL/min; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol] to give the title compound as a white solid. MS (ES+) *m/z*: 322 $(M+H)^+$.

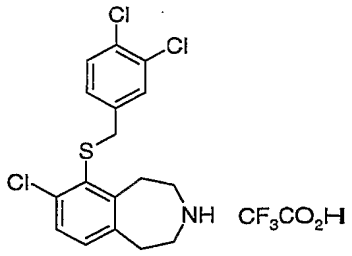
Examples 385-386 may be prepared essentially as described in Example 384 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.



Ex.	R	Compound	MS (ES+) *m/z*
385	4-Cl	7-Chloro-6-(4-chloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	338 $(M+H)^+$
386	4-CN	7-Chloro-6-(4-cyano-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	329 $(M+H)^+$

Example 387

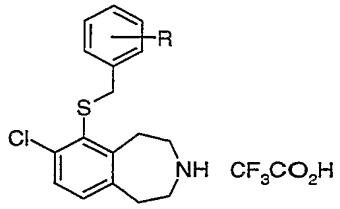
7-Chloro-6-(3,4-dichlorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



To a 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (200 mg, 0.521 mmol) in methanol (3.3 mL) under nitrogen add potassium hydroxide (0.9 g, 16.07 mmol) at ambient temperature. When the mixture becomes homogenous, heat at 55-60°C for 2-3 h, until TLC shows the disappearance of starting material. Cool to ambient temperature,

add aqueous saturated ammonium chloride solution, extract three times with diethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in anhydrous DCM (5 mL) under nitrogen. Add PS-DIEA (Argonaut, 3.83 mmol/g, 410 mg, 1.57 mmol) and 3,4-dichlorobenzyl bromide (100 µL, 0.586 mmol) at ambient temperature and allow the reaction to continue overnight. Filter the reaction mixture from the resin and rinse with DCM (2 mL), methanol (2 mL), DCM (2 mL), and methanol (2 mL). Concentrate *in vacuo*. Treat a solution of the crude 3-*tert*-butoxycarbonyl-7-chloro-6-(3,4-dichloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in DCM (2 mL) with a 2M hydrogen chloride in ether (excess) and continue stirring until TLC shows consumption of starting material. Concentrate *in vacuo* and triturate the obtained solid with ether:pentane (10:90). Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min) to give the title compound as a white solid (97 mg, 38%). MS (APCI+) *m/z*: 374 $(M+H)^+$.

Examples 388-393 may be prepared essentially as described in Example 387 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.

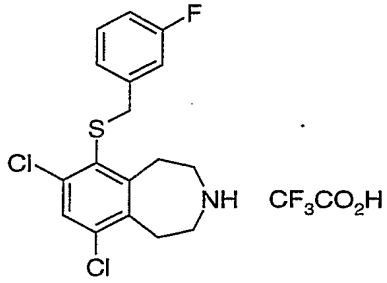


Ex.	R	Compound	MS (ES+ or APCI+)
388	3-Cl	7-Chloro-6-(3-chloro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	338 $(M+H)^+$
389	3-F	7-Chloro-6-(3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	322 $(M+H)^+$

Ex.	R	Compound	MS (ES+ or APCI+)
390	3,4-diF	7-Chloro-6-(3,4-difluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	340 $(M+H)^+$
391	3,5-diF	7-Chloro-6-(3,5-difluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	340 $(M+H)^+$
392	3,4,5-triF	7-Chloro-6-(3,4,5-trifluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	358 $(M+H)^+$
393	3-OCF_3	7-Chloro-6-(3-trifluoromethoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate	388 $(M+H)^+$

Example 394

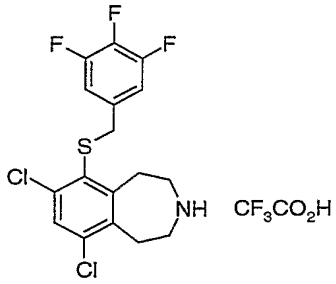
7,9-Dichloro-6-(3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 3-fluorobenzyl bromide, using a method similar to the Example 387. Deprotect and isolate the title compound as a white solid after preparative reverse phase HPLC. MS (ES+) *m/z*: 356 $(M+H)^+$.

Example 395

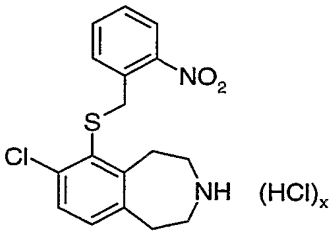
7,9-Dichloro-6-(3,4,5-trifluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 3,4,5-trifluorobenzyl bromide, using a method similar to the Example 387. Deprotect and isolate the title compound as a white solid after preparative reverse phase HPLC. MS (APCI+) *m/z*: 392 $(M+H)^+$.

Example 396

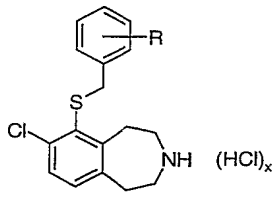
7-Chloro-6-(2-nitro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxylcarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine and 2-nitrobenzyl bromide to give, after chromatography eluting with hexane/EtOAc (10:1) and deprotection by the General Procedure 1-4, the title compound as an off-white powder. MS (APCI+) *m/z*: 349 $(M+H)^+$.

Examples 397-399 may be prepared essentially as described in Example 396 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-

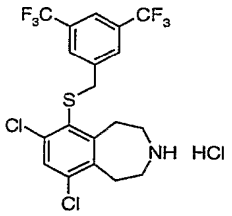
benzo[*d*]azepine and the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.



Ex.	R	Compound	MS (ES+ or APCI+)
397	2-OCF_3	7-Chloro-6-(2-trifluoromethoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	388 $(M+H)^+$
398	3-OPh	7-Chloro-6-(3-phenoxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	396 $(M+H)^+$
399	3,5-diCF_3	7-Chloro-6-(3,5-bistrifluoromethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	440 $(M+H)^+$

Example 400

7,9-Dichloro-6-(3,5-*bis*-trifluoromethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride (2148393)

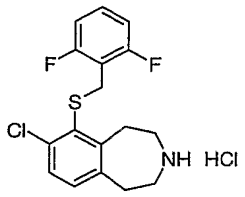


Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with 3,5-bis-trifluoromethylbenzyl bromide, using a method similar to the Example 396. Deprotect the crude mixture and purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate; solvent B: acetonitrile; 30-100% B over 20 minutes;

flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 474 $(M+H)^+$.

Example 401

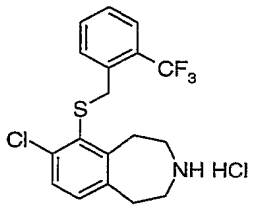
7-Chloro-6-(2,6-difluorobenzylthio-)2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2,6-difluorobenzyl bromide to give, after deprotection by the General Procedure 1-4, the title compound.

Example 402

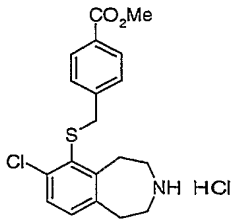
7-Chloro-6-(2-trifluoromethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 2-trifluoromethylbenzyl bromide. Use a method similar to the General Procedure 1-4 to give the title compound as a waxy tan solid. MS (APCI+) *m/z*: 372 $(M+H)^+$.

Example 403

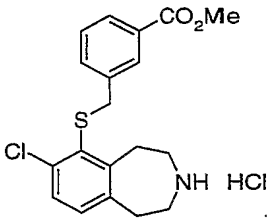
7-Chloro-6-(4-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl 4-(bromomethyl)benzoate to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 362 $(M+H)^+$.

Example 404

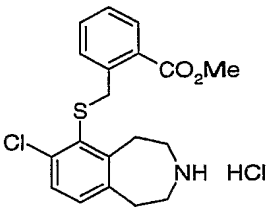
7-Chloro-6-(3-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with methyl 3-(bromomethyl)benzoate. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-2 to give the title compound. MS (APCI+) *m/z*: 362 $(M+H)^+$.

Example 405

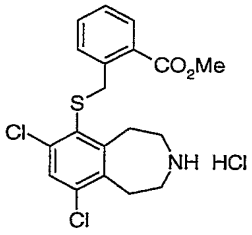
7-Chloro-6-(2-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with methyl 2-(bromomethyl)benzoate. Use a method similar to the General Procedure 1-4 and purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate, solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2, to give the title compound as a white solid. MS (ES+) *m/z*: 362 $(M+H)^+$.

Example 406

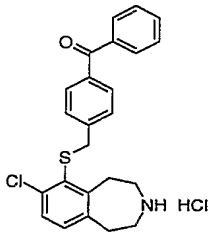
7,9-Dichloro-6-(2-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 405, after preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate; solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 396 $(M+H)^+$.

Example 407

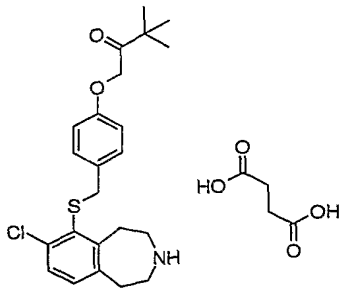
6-(4-Benzoylbenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 380 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 4-(bromomethyl)benzophenone. Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (ES+) *m/z*: 408 $(M+H)^+$.

Example 408

7-Chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

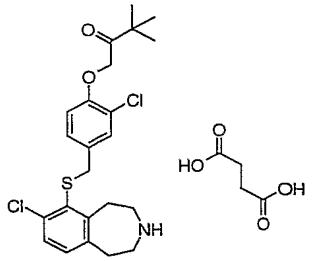


Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (577 mg, 1.5 mmol) and 1-(4-bromomethylphenoxy)-3,3-dimethylbutan-2-one (556 mg, 1.95 mmol) to give, after chromatography on silica gel eluting with EtOAc/hexane (1:5), 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (669 mg, 86%). MS (ES+) *m/z*: 518 $(M+H)^+$.

Use a method similar to the General Procedure 1-5 to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (669 mg, 1.29 mmol). Purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (92:8) to give the free base of the title compound as a colorless oil (349 mg, 64%). MS (ES+) *m/z*: 418 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound.

Example 409

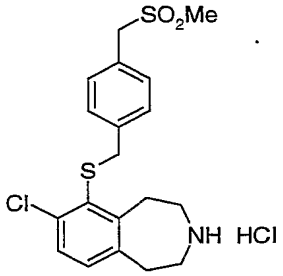
7-Chloro-6-[3-chloro-4-(3,3-dimethyl-2-oxo-butoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 408, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-(4-bromomethyl-3-chlorophenoxy)-3,3-dimethylbutan-2-one to give the title compound. MS (ES+) *m/z*: 452 $(M+H)^+$.

Example 410

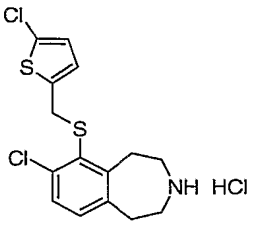
7-Chloro-6-(4-methanesulfonylmethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-chloro-6-(4-methanesulfonylmethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 396 $(M+H)^+$.

Example 411

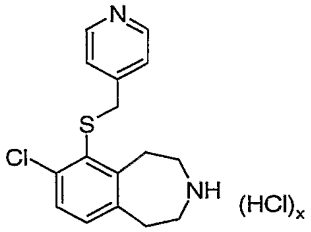
7-Chloro-6-(5-chloro-thiophen-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloro-5-(chloromethyl)thiophene to give, after hydrochloride formation by the General Procedure 2-2, the title compound as a brown solid. MS (APCI+) *m/z*: 344 $(M+H)^+$.

Example 412

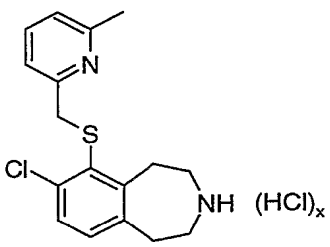
7-Chloro-6-(pyridin-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-bromomethylpyridine hydrobromide to give, after hydrochloride formation by the General Procedure 2-2, the title compound as a white solid. MS (APCI+) *m/z*: 305 $(M+H)^+$.

Example 413

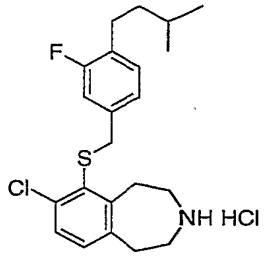
7-Chloro-6-(6-methyl-pyridin-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-chloromethyl-6-methylpryidine to give, after chromatography on silica gel eluting with hexane/EtOAc (4:1) and deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 319 $(M+H)^+$.

Example 414

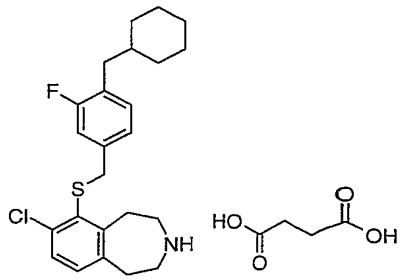
7-Chloro-6-[3-fluoro-4-(3-methylbutyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (0.210 mg, 0.42 mmol) and dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct (17 mg, 0.021 mmol) add 0.5 M 3-methylbutylzinc bromide in THF (4.2 mL, 2.10 mmol). Degas, purge with dry nitrogen, and stir overnight at 80 °C. Cool to ambient temperature, dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[3-fluoro-4-(3-methylbutyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (85 mg, 42%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 392 $(M+H)^+$.

Example 415

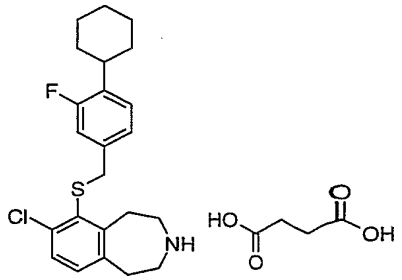
7-Chloro-6-(4-cyclohexylmethyl-3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 414 to react 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine with (cyclohexyl)methylzinc bromide. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (ES+) *m/z*: 418 $(M+H)^+$.

Example 416

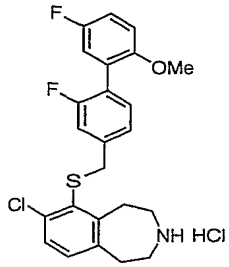
7-Chloro-6-(4-cyclohexyl-3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 414, using 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and cyclohexylzinc bromide. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (ES+) *m/z*: 404 $(M+H)^+$.

Example 417

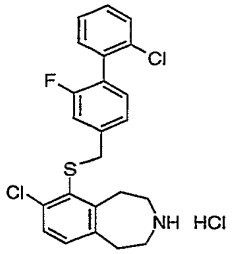
7-Chloro-6-(2,5'-difluoro-2'-methoxybiphenyl-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Degas a stirred mixture of 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (212 mg, 0.424 mmol), 5-fluoro-2-methoxybenzene boronic acid (108 mg, 0.636 mmol), potassium carbonate (292 mg, 2.12 mmol), triphenylphosphine (11 mg, 0.0424 mmol) and bis(triphenylphosphine)-palladium(II) chloride (15 mg, 0.0212 mmol) in dioxane (3 mL) and water (1 mL). Purge with dry nitrogen and heat at 100 °C for 5 h. Cool to ambient temperature, add water, extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/ EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2,5'-difluoro-2'-methoxy-biphenyl-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as yellow oil (216 mg, 93%). Use a method similar to the General Procedure 1-4 to give the title compound as a yellow foam. MS (ES+) *m/z*: 446 $(M+H)^+$.

Example 418

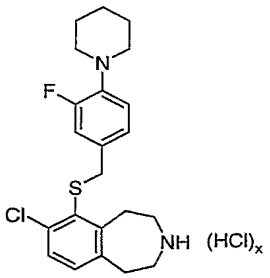
7-Chloro-6-(2'-chloro-2-fluorobiphenyl-4-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 417, using 2-chlorophenylboronic acid to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 432 $(M+H)^+$.

Example 419

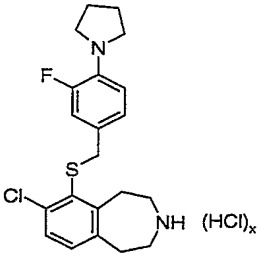
7-Chloro-6-(3-fluoro-4-piperidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



In a sealed tube, add tris(dibenzylideneacetone)dipalladium (13 mg, 0.014 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19 mg, 0.029 mmol) to a mixture of 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (957 mg, 1.91 mmol), sodium *tert*-butoxide (367 mg, 3.83 mmol), 18-crown-6 (50 mg, 0.191 mmol) and piperidine (944 µl, 9.57 mmol) in toluene (10 mL). Flush the mixture with nitrogen and heat overnight. Cool to ambient temperature, dilute with water and extract three times with EtOAc. Dry over anhydrous Na_2SO_4 and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-piperidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (511 mg, 33%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 405 $(M+H)^+$.

Example 420

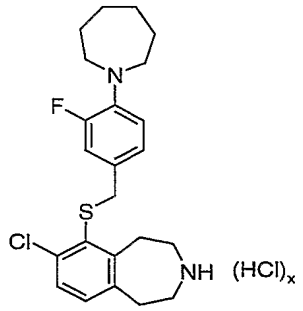
7-Chloro-6-(3-fluoro-4-pyrrolidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 419 to react 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine with pyrrolidine. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 391 $(M+H)^+$.

Example 421

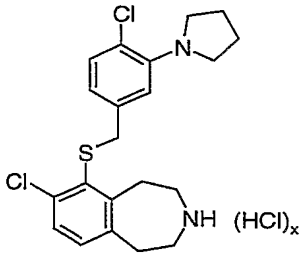
6-(4-Azepan-1-yl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 419 to react 6-(4-bromo-3-fluorobenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine with homopiperidine. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 419 $(M+H)^+$.

Example 422

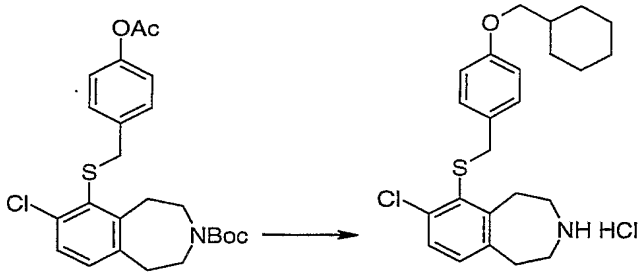
7-Chloro-6-(4-chloro-3-pyrrolidin-1-yl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride



Use a method similar to the Example 419, using 6-(3-bromo-4-chloro-benzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyrrolidine to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 407 $(M+H)^+$.

Example 423

7-Chloro-6-(4-cyclohexylmethoxybenzylthio)-3-*tert*-butoxycarbonyl- -2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

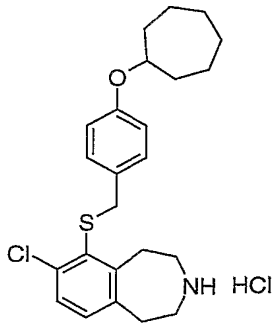


Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-(chloromethyl)phenyl acetate to give 6-(4-acetoxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a white solid.

To 6-(4-acetoxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (532 mg, 1.15 mmol) in methanol (8 mL) at ambient temperature add with stirring a solution of potassium carbonate (796 mg, 5.77 mmol) in water (4 mL) and stir the mixture for 2 h. Dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. To a portion of the crude phenol thus obtained (204 mg, 0.487 mmol) in THF (5 mL), add with stirring diisopropyl azodicarboxylate (216 µl, 1.71 mmol) followed by triphenylphosphine (306 mg, 1.17 mmol) and cyclohexylmethanol (619 mg, 5.42 mmol). Heat at 60°C for 3 h, cool to ambient temperature and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-cyclohexylmethoxy-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (176 mg, 70%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 416 $(M+H)^+$.

Example 424

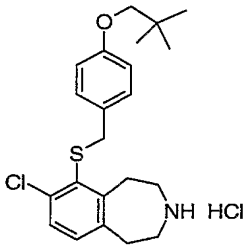
7-Chloro-6-(4-cycloheptyloxybenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 423 to react 6-(4-acetoxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with cycloheptanol. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 416 $(M+H)^+$.

Example 425

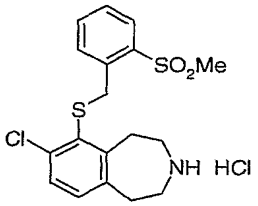
7-Chloro-6-[4-(2,2-dimethylpropoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromomethyl-4-(2,2-dimethylpropoxy)-benzene. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 390 $(M+H)^+$.

Example 426

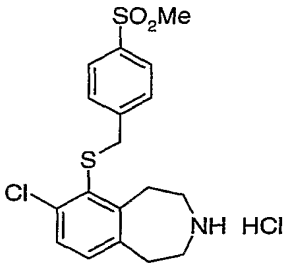
7-Chloro-6-(2-methanesulfonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromomethyl-2-methanesulfonyl-benzene to give, after deprotection by the General Procedure 1-4, the title compound and as a white solid. MS (APCI+) *m/z*: 382 $(M+H)^+$.

Example 427

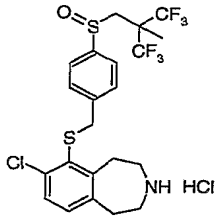
7-Chloro-6-(4-methanesulfonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 380, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-methylsulfonylbenzyl bromide to give, after hydrochloride formation by the General Procedure 2-2, the title compound as a white solid. MS (ES+) *m/z*: 382 $(M+H)^+$.

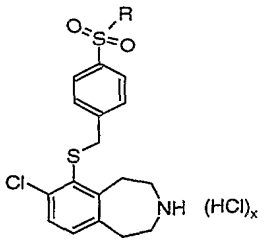
Example 428

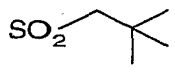
7-Chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfinyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

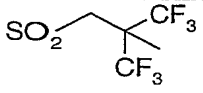
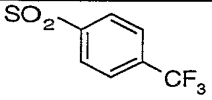
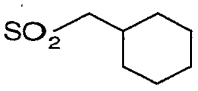


To 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (723 mg, 1.88 mmol) in methanol (10 mL) add potassium hydroxide pellets (3.34 g, 60.2 mmol) and stir mixture at 50 °C for 2 h. Cool to ambient temperature, add aqueous saturated ammonium chloride, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Dissolve the compound in DMF (5 mL), add cesium carbonate (920 mg, 2.82 mmol) and 1-bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propane-1-sulfinyl)-benzene (824 mg, 2.071 mmol) and stir 2 h at ambient temperature. Dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propane-1-sulfinyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a yellow oil (986 mg, 83%). Use a method similar to the General Procedure 1-4 to give the title compound as a white foam. MS (ES+) *m/z*: 530 $(M+H)^+$.

Examples 429-432 may be prepared essentially as described in Example 428 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriately substituted benzyl bromide. MS (ES+) data are included in the Table below.

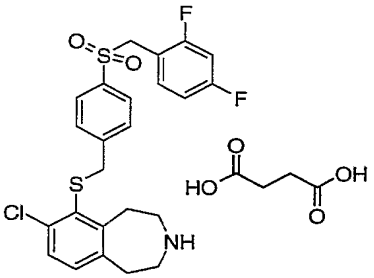


Ex.	SO_2R	Compound	MS (ES+ or APCI+)
429		7-Chloro-6-[4-(2,2-dimethyl-propane-1-sulfonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	438 $(M+H)^+$

Ex.	SO_2R	Compound	MS (ES+ or APCI+)
430		7-Chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropane-1-sulfonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	546 $(M+H)^+$
431		7-Chloro-6-[4-(4-trifluoromethyl-benzenesulfonyl)-benzylthio]-1,2,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride	512 $(M+H)^+$
432		7-Chloro-6-(4-cyclohexylmethanesulfonyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	464 $(M+H)^+$

Example 433

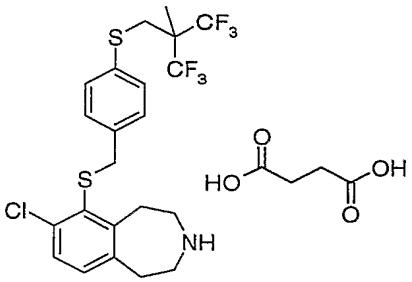
7-Chloro-6-[4-(2,4-difluoro-phenylmethanesulfonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 428 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-(4-bromomethyl-benzenesulfonylmethyl)-2,4-difluoro-benzene. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (ES+) *m/z*: 494 $(M+H)^+$.

Example 434

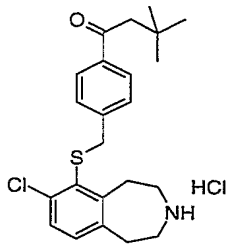
7-Chloro-6-[4-(3,3,3-trifluoro-2-methyl-2-trifluoromethylpropylthio)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 428 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-bromomethyl-4-(3,3,3-trifluoro-2-methyl-2-trifluoromethyl-propylthio)-benzene. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-1, to give the title compound as a white solid. MS (APCI$^+$) *m/z*: 514 $(M+H)^+$.

Example 435

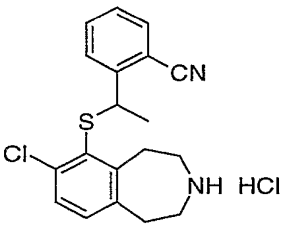
7-Chloro-6-[4-(3,3-dimethylbutyryl)-benzylthio]-1,2,4,5-tetrahydro-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 428 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 1-(4-bromomethylphenyl)-3,3-dimethylbutan-1-one. Use a method similar to the General Procedure 1-4, basic workup, and a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI$^+$) *m/z*: 402 $(M+H)^+$.

Example 436

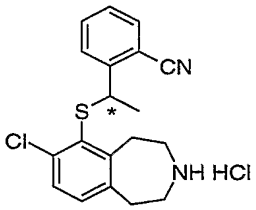
(±)-7-Chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (±)-2-(1-bromoethyl)benzonitrile to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 343 $(M+H)^+$.

Example 437

(-)-7-Chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



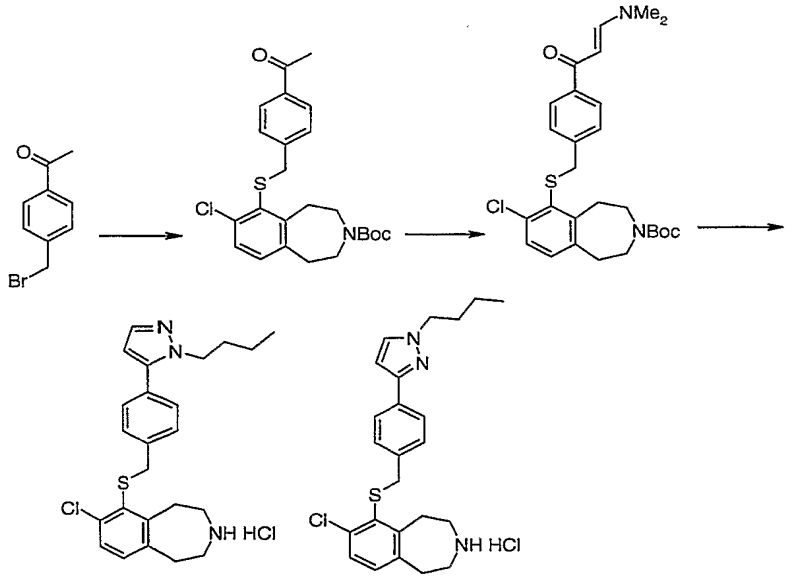
Dissolve (±)-7-chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine succinate (326 mg, 1.0 mmol) in DCM (5 mL) and pyridine (0.4 mL, 5 mmol). Add di-*tert*-butyl-dicarbonate (270 mg, 1.2 mmol) and stir the mixture for 16 h at ambient temperature. Wash the mixture with 5N aqueous NaOH and saturated aqueous $NaHCO_3$ successively. Collect the organic layer and concentrate *in vacuo*. Purify the residue by chromatography on silica gel eluting with hexane/EtOAc (1:1) to obtain (±)-3-*tert*-butoxycarbonyl-7-chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (393 mg, 93%). Separate the enantiomers of (±) 3-*tert*-butoxycarbonyl-7-chloro-6-[1-(2-cyanophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralpak AD 8x30 cm column, eluting with heptane/isopropylamine, 95:5).

Take the second eluting isomer and deprotect using the General Procedure 1-5. Purify with SCX chromatography. Use a method similar to the General Procedure 2-2 to

obtain the title compound (125 mg, 37%). MS (ES+) *m/z*: 343 $(M+H)^+$. $[\alpha]^{20}_D$ -112° (c 0.5, CH_3OH).

Examples 438 and 439

6-[4-(2-Butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride and 6-[4-(1-Butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



4-Acetylbenzyl bromide: Use a method similar to the Preparation 184, using 4-methylacetophenone, to give the desired intermediate as a white solid.

6-(4-Acetylbenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Example 380, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-acetylbenzyl bromide to give, after chromatography eluting with hexane/EtOAc (15:1), the desired intermediate as a white solid. MS (APCI+) *m/z* 346 $(M+H\text{-}Boc)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-[4-(3-dimethylaminoacryloyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a solution of 6-(4-acetylbenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.0 g, 2.2 mmol) in

toluene (10 mL) at 110 °C overnight in the presence of *tert*-butoxy-bis(dimethylamino)-methane (1.0 mL, 4.84 mmol). Concentrate *in vacuo* to provide the desired intermediate as a dark oil (1.2 g, 100%). MS (APCI+) *m/z* 401 $(M+H\text{-}Boc)^+$.

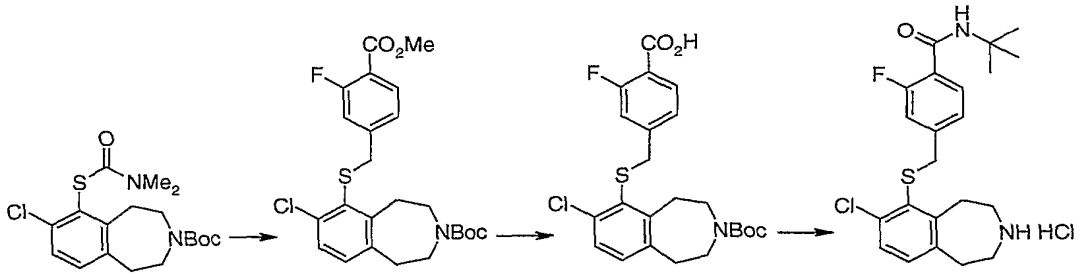
6-[4-(1-Butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: To a stirred mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-[4-(3-dimethylaminoacryloyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (240 mg, 0.475 mmol), butylhydrazine oxalate (102 mg, 0.574 mmol), sodium carbonate (55 mg, 0.444 mmol) in water (8 mL) and methanol (10 mL) add acetic acid (ca. 3-6 drops) to pH 5. Heat overnight at 70 °C. Concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (10:1) to give a mixture of the desired intermediates, 3-*tert*-butoxycarbonyl-6-[4-(2-butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (65 mg, 32%), MS (APCI+) *m/z*: 426 $(M+H\text{-}Boc)^+$ and 3-*tert*-butoxycarbonyl-6-[4-(1-butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (100 mg, 50%), MS (APCI+) *m/z*: 426 $(M+H\text{-}Boc)^+$.

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-6-[4-(2-butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give 6-[4-(2-butyl-2*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (Example 438) as a white solid. MS (APCI+) *m/z*: 426 $(M+H)^+$.

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-6-[4-(1-butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give 6-[4-(1-butyl-1*H*-pyrazol-3-yl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (Example 439) as a white solid. MS (APCI+) *m/z*: 426 $(M+H)^+$.

Example 440

6-(4-*tert*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

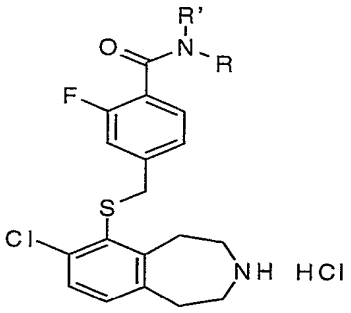


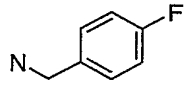
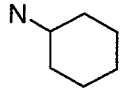
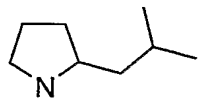
3-*tert*-Butoxycarbonyl-7-chloro-6-(3-fluoro-4-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Example 428, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl 4-bromomethyl-2-fluorobenzoate, to give the desired intermediate as a white solid.

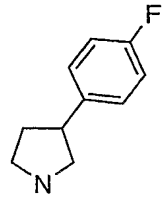
3-*tert*-Butoxycarbonyl-6-(4-carboxy-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Heat a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(3-fluoro-4-methoxycarbonylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (3.56 g, 7.44 mmol) in THF (50 mL) and water (40 mL) overnight at 65 °C in the presence of potassium hydroxide (8.30 g, 148.77 mmol). Cool the mixture to 0 °C, add slowly a 1N solution of hydrochloric acid until pH 5. Extract three times with EtOAc, dry over anhydrous Na_2SO_4 and concentrate *in vacuo* to provide the desired intermediate as a white solid (3.5 g, 99%).

6-(4-*tert*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: To a solution of 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.1 g, 2.36 mmol) in DMF (7 mL), add *tert*-butylamine (12.05 g, 165.2 mmol), EDC (1.81 g, 9.44 mmol) and HOBt (1.44g, 10.62 mmol) and stir in a sealed tube at 70 °C overnight. Dilute with EtOAc, wash with water, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-6-(4-*tert*-butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil. MS (APCI+) *m/z*: 421 $(M+H)^+$. Use a method similar to the General Procedure 1-4 to give the title compound as a white powder. MS (APCI+) *m/z*: 421 $(M+H)^+$.

Examples 441-447 may be prepared essentially as described in Example 440 by reacting 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriate amine. MS (ES+) data are included in the Table below.

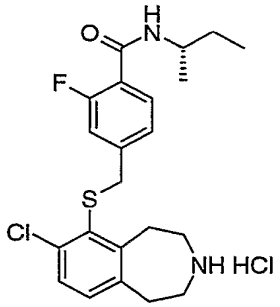


Ex.	N-R	R'	Compound	MS (ES+ or APCI+)
441	N-(*n*-Pr)	H	7-Chloro-6-(3-fluoro-4-*n*-propylcarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	407 $(M+H)^+$
442	N-(*i*-Bu)	H	6-(4-*iso*-Butylcarbamoyl-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	421 $(M+H)^+$
443	N-(*n*-Pr)	*n*-Pr	7-Chloro-6-(4-dipropylcarbamoyl-3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	449 $(M+H)^+$
444		H	7-Chloro-6-[3-fluoro-4-(4-fluoro-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	473 $(M+H)^+$
445		H	7-Chloro-6-(4-cyclohexylcarbamoyl-3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	447 $(M+H)^+$
446			7-Chloro-6-[3-fluoro-4-(2-isobutyl-pyrrolidine-1-carbonyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	475 $(M+H)^+$

Ex.	N-R	R'	Compound	MS (ES+ or APCI+)
447			7-Chloro-6-{3-fluoro-4-[3-(4-fluoro-phenyl)-pyrrolidine-1-carbonyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine-Hydrochloride	513 $(M+H)^+$

Example 448

(*S*)-(+)-6-(4-*sec*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

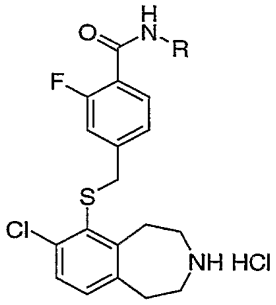


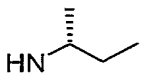
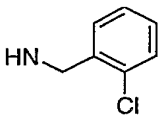
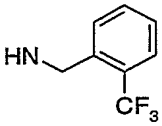
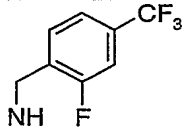
3-*tert*-Butoxycarbonyl-7-chloro-6-(4-chlorocarbonyl-3-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.95 g, 4.21 mmol) in DCM (20 mL) at 0 °C under nitrogen, add three drops of DMF and oxalyl chloride (1.06 g, 8.41 mmol). Stir for 2 h and concentrate *in vacuo* to afford the desired intermediate as a yellow oil (1.93 g, 95%).

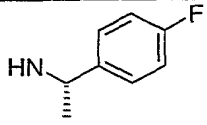
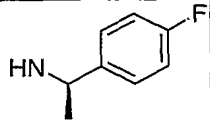
(*S*)-3-*tert*-Butoxycarbonyl-6-(4-*sec*-butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1H-benzo[*d*]azepine: To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(4-chlorocarbonyl-3-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (415 mg, 0.860 mmol) in DCM (10 mL), add (*S*)-(+)-*sec*-butylamine (1.0 g, 13.7 mmol) and stir at ambient temperature for 30 min. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give the desired intermediate as a pale oil (352 mg, 79%). MS (APCI+) *m/z*: 421 $(M+H\text{-Boc})^+$.

(*S*)- (+)-6-(4-*sec*-Butylcarbamoyl-3-fluorobenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride: Use a method similar to the General Procedure 1-4, using (+)-3-*tert*-butoxycarbonyl-6-(4-*sec*-butylcarbamoyl-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a pale solid. MS (APCI+) *m/z*: 421 $(M+H)^+$. $[\alpha]^{20}_D$ +8.7° (c 0.5, CH_3OH).

Examples 449-454 may be prepared essentially as described in Example 448 by reacting 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with the appropriate amine. Optical rotation and MS (ES+) data are included in the Table below.

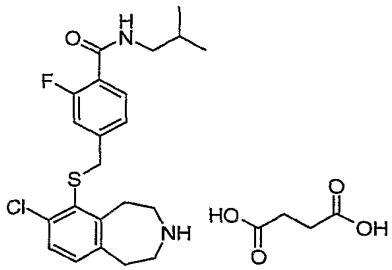


Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent	MS (ES+) *m/z*
449		*(R)*-(-)-6-(4-*sec*-Butylcarbamoyl-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	-7.0° (c 0.5, CH_3OH).	421 $(M+H)^+$
450		7-Chloro-6-[4-(2-chloro-benzylcarbamoyl)-3-fluoro-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	-	489 $(M+H)^+$
451		7-Chloro-6-[3-fluoro-4-(2-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-3-Hydrochloride	-	523 $(M+H)^+$
452		7-Chloro-6-[3-fluoro-4-(2-fluoro-4-trifluoromethyl-benzyl-carbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]aze-pine Hydrochloride	-	541 $(M+H)^+$

Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent	MS (ES+) *m/z*
453		(*S*)-(-)-7-Chloro-6-{3-fluoro-4-[1-(4-fluoro-phenyl)-ethyl-carbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo-[*d*]azepine Hydrochloride	-25.8° (c 0.5, CH_3OH)	487 $(M+H)^+$
454		(*R*)-(+)-7-Chloro-6-{3-fluoro-4-[1-(4-fluoro-phenyl)-ethyl-carbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo-[*d*]azepine Hydrochloride	+24.9° (c 0.5, CH_3OH)	487 $(M+H)^+$

Example 455

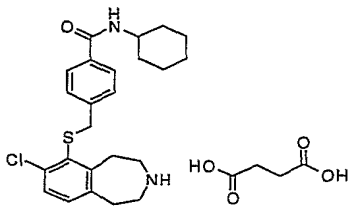
7-Chloro-6-(3-fluoro-4-isobutylcarbamoyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



Use a method similar to the Example 448 to react 3-*tert*-butoxycarbonyl-6-(4-carboxy-3-fluoro-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with isobutylamine. Use a method similar to the General Procedure 1-4, basic work-up, and a method similar to the General Procedure 2-1 to give the title compound as a white solid. MS (ES+) *m/z*: 403 $(M+H)^+$.

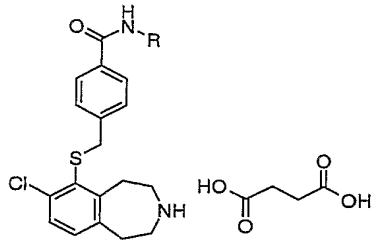
Example 456

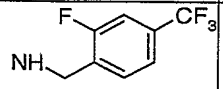
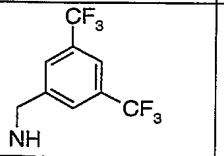
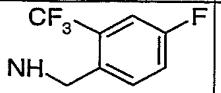
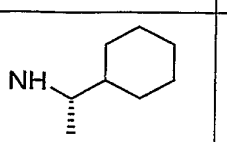
7-Chloro-6-(4-cyclohexylcarbamoylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

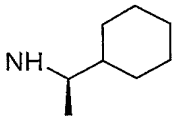
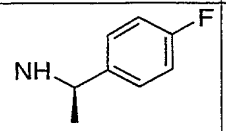
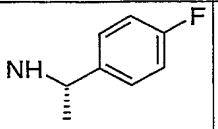
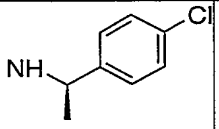
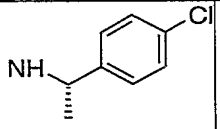


Use a method similar to the Preparation 177 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 4-chloromethyl-*N*-cyclohexylbenzamide. Use a method similar to the General Procedure 1-5, basic workup, and a method similar to the General Procedure 2-1 to give the title compound as a white solid. MS (ES+) *m/z*: 429 $(M+H)^+$.

Examples 457-465 may be prepared essentially as described in Example 456 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl chloride. Optical rotation and MS (ES+) data are included in the Table below.

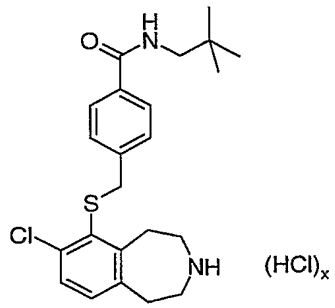


Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent)	MS (ES+ or APCI+)
457		7-Chloro-6-[4-(2-fluoro-4-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-	523 $(M+H)^+$
458		[4-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-benzylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-	573 $(M+H)^+$
459		7-Chloro-6-[4-(4-fluoro-2-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-	523 $(M+H)^+$
460		(*S*)-(+)-7-Chloro-6-[4-(1-cyclohexyl-ethylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	+11.2° (c 0.5, CH_3OH)	457 $(M+H)^+$

Ex.	NH-R	Compound	$[\alpha]^{20}_D$ (c, solvent)	MS (ES+ or APCI+)
461		(*R*)-(-)-7-Chloro-6-[4-(1-cyclohexyl-ethylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-11.3° (c 0.5, CH_3OH)	457 $(M+H)^+$
462		(*R*)-(+)-7-Chloro-6-{4-[1-(4-fluoro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	+2.2° (c 0.5, CH_3OH)	469 $(M+H)^+$
463		(*S*)-(-)-7-Chloro-6-{4-[1-(4-fluoro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-1.6° (c 0.5, CH_3OH)	469 $(M+H)^+$
464		(*R*)-(-)-7-Chloro-6-{4-[1-(4-chloro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	-5.8° (c 0.5, CH_3OH)	485 $(M+H)^+$
465		(*S*)-(+)-7-Chloro-6-{4-[1-(4-chloro-phenyl)-ethylcarbamoyl]-benzylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate	+5.5° (c 0.5, CH_3OH)	485 $(M+H)^+$

Example 466

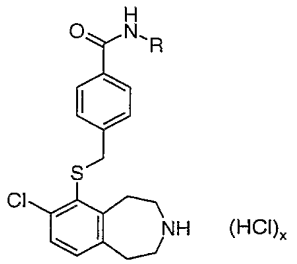
7-Chloro-6-[4-(2,2-dimethyl-propylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

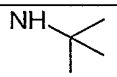
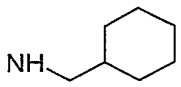
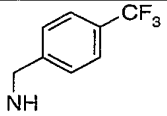
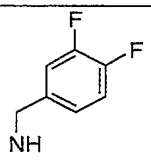
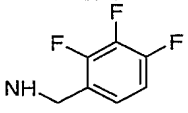


Use a method similar to the Example 456, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-chloromethyl-*N*-

(2,2-dimethyl-propyl)-benzamide to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 417 $(M+H)^+$.

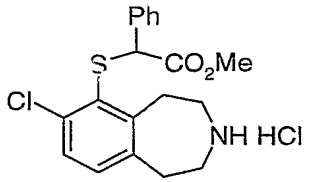
Examples 467-471 may be prepared essentially as described in Example 466 by using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and the appropriately substituted benzyl chloride. MS (ES+) data are included in the Table below.



Ex.	NH-R	Compound	MS (ES+) *m/z*
467		6-(4-*tert*-Butylcarbamoyl-benzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	403 $(M+H)^+$
468		7-Chloro-6-[4-(cyclohexylmethyl-carbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	443 $(M+H)^+$
469		7-Chloro-6-[4-(4-trifluoromethyl-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	505 $(M+H)^+$
470		7-Chloro-6-[4-(3,4-difluoro-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	473 $(M+H)^+$
471		7-Chloro-6-[4-(2,3,4-trifluoro-benzylcarbamoyl)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride	491 $(M+H)^+$

Example 472

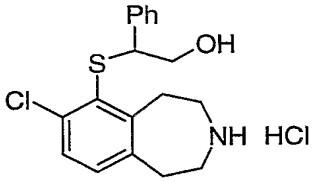
(±)-7-Chloro-6-(1-methoxycarbonyl-1-phenyl-methyllthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using (±)-3-*tert*-butoxycarbonyl-7-chloro-6-(1-methoxycarbonyl-1-phenyl-methyllthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z* 362 $(M+H)^+$.

Example 473

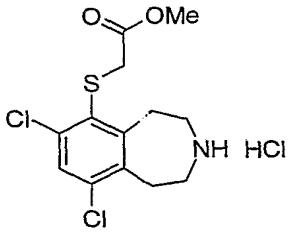
(±)-7-Chloro-6-(2-hydroxy-1-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of (±)-3-*tert*-butoxycarbonyl-6-(1-carboxy-1-phenyl-methyllthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (220 mg, 0.447 mmol) in THF (10 mL) at 0° C, add a solution of 1M borane in THF (1.4 mL, 1.4 mmol). Continue stirring for 2 h at 0° C and then overnight at ambient temperature. Quench by slow addition of methanol, stir 1 h at ambient temperature and concentrate *in vacuo*. Add aqueous saturated ammonium chloride, extract three times with EtOAc, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 474

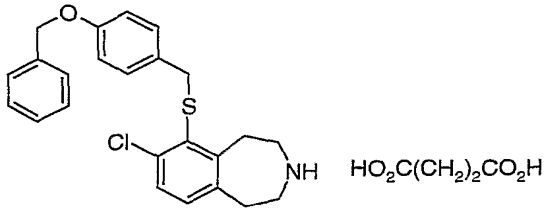
7,9-Dichloro-6-methoxycarbonylmethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain as minor product from the reaction of the 4:1 mixture of 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 3-*tert*-butoxycarbonyl-7,9-dichloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-benzo[*d*]azepine with methyl bromoacetate, using a method similar to the Example 347. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 320 $(M+H)^+$.

Example 475

6-(4-Benzyloxybenzylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



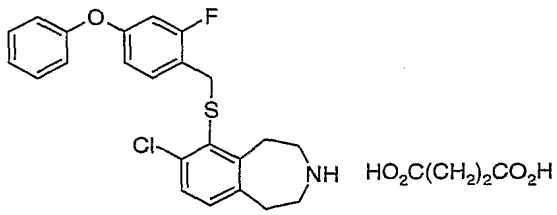
Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (706 mg, 1.84 mmol) in methanol (20 mL). Add potassium hydroxide (3.5 g, 55 mmol) and heat the mixture at reflux for 3h. Cool to ambient temperature. Pour reaction in saturated aqueous NH_4Cl solution. Extract three times with EtOAc. Combine organic extracts, dry over Na_2SO_4 and concentrate *in vacuo* to obtain crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (602 mg, 100%). Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (282 mg, 0.9 mmol) in acetone (30 mL). Add 4-benzyloxybenzyl chloride (251 mg, 1.08 mmol), potassium carbonate (powder) (373 mg, 2.7 mmol) and potassium iodide (powder) (15 mg, 0.1 mmol) and reflux for 16 h. Cool the reaction to ambient temperature, dilute with acetone, filter and concentrate *in vacuo*.

Purify by chromatography on silica gel eluting with hexane/EtOAc (1:0 and 17:3) to give 6-(4-benzyloxybenzylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (309 mg, 67%). MS (ES+) *m/z*: 510 $(M+H)^+$.

Use a method similar to the General Procedure 1-4 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to obtain the free base of the title compound (230 mg, 92%). MS (ES+) *m/z*: 410 (M+H)+. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Example 476

7-Chloro-6-[(2-fluoro-4-phenoxy)benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

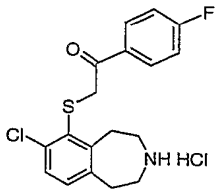


Use a method similar to the Example 475, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 1-bromomethyl-2-fluoro-4-phenoxybenzene to provide, after chromatography on silica gel eluting with hexane/EtOAc (85:15), 3-*tert*-butoxycarbonyl-7-chloro-6-[(2-fluoro-4-phenoxy)-benzylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (384 mg, 83%). MS (ES+) *m/z*: 414 $(M\text{-}Boc+2H)^+$.

Use a method similar to the General Procedure 1-4 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to obtain the free base of the title compound (203 mg, 65%). MS (ES+) *m/z*: 414 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to obtain the title compound.

Example 477

7-Chloro-6-[2-(4-fluorophenyl)-2-oxo-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

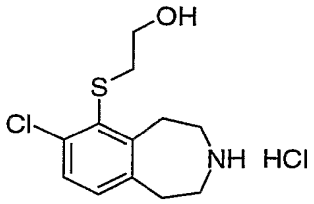


Use a method similar to the Example 475, using crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromo-4'-fluoroacetophenone (239 mg, 1.1 mmol) to provide, after stirring at ambient temperature for 16 h and purification by chromatography on silica gel eluting with hexane/EtOAc (4:1), 3-*tert*-butoxycarbonyl-7-chloro-6-[2-(4-fluorophenyl)-2-oxo-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (38 mg, 9%).

Use a method similar to the General Procedure 1-5 and purify by chromatography on silica gel eluting with DCM/2M ammonia in methanol (95:5) to obtain the free base of the title compound (23 mg, 78%). MS (ES+) *m/z*: 350 $(M+H)^+$. Use a method similar to the General Procedure 2-2 to obtain the title compound.

Example 478

7-Chloro-6-(2-hydroxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl bromoacetate to give 3-*tert*-butoxycarbonyl-7-chloro-6-methoxycarbonylmethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

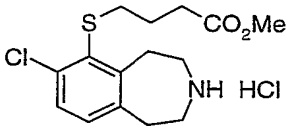
To a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-methoxycarbonylmethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (750 mg, 1.94 mmol) in THF (25 mL) at –78 °C under nitrogen, add 1M DIBAL in toluene (5.0 mL, 5.0 mmol) dropwise with stirring. Warm to –30°C over 1 h and quench carefully with water. Extract with EtOAc, dry over

anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (4:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (651 mg, 94%).

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (190 mg, 0.531 mmol) to give the title compound as a white solid (105 mg, 67%). MS (ES+) *m/z*: 258 $(M+H)^+$.

Example 479

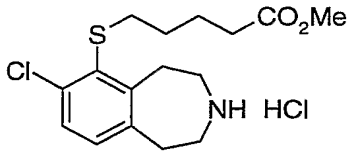
7-Chloro-6-(3-methoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 347, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and methyl 4-bromobutyrate to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 314 $(M+H)^+$.

Example 480

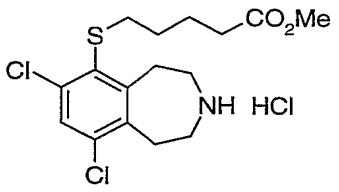
7-Chloro-6-(4-methoxycarbonyl -butylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with methyl-5-bromovalerate. Purify by preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to give the title compound as a white solid. MS (APCI+) *m/z*: 328 $(M+H)^+$.

Example 481

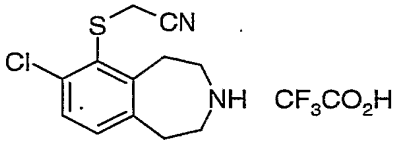
7,9-Dichloro-6-(4-methoxycarbonylbutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 480, after preparative TLC eluting with 19:1 DCM/saturated ammonia in methanol. Use a method similar to the General Procedure 2-2 to obtain the title compound as a pale yellow solid. MS (APCI+) *m/z*: 362 $(M+H)^+$.

Example 482

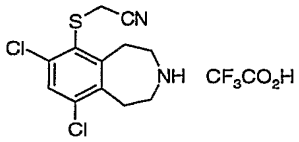
7-Chloro-6-cyanomethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 387 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with bromoacetonitrile. Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min) to give the title compound as a white solid. MS (APCI+) *m/z*: 253 $(M+H)^+$.

Example 483

6-Cyanomethylthio-7,9-dichloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Obtain the title compound as a minor product from Example 482, after preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; solvent A: 10 mM aqueous ammonium carbonate, solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). MS (APCI+) *m/z*: 287 $(M+H)^+$.

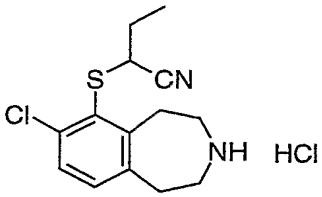
Example 484

(±)-7-Chloro-6-(1-cyanoethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-bromopropionitrile to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 267 $(M+H)^+$.

Example 485

(±)-7-Chloro-6-(1-cyanopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

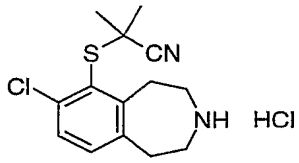


To a stirred solution of 1.5M lithium diisopropylamide in cyclohexane (1.37 mL, 2.05 mmol) in dry THF (5 mL) at –78 °C under dry nitrogen, add a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-cyanomethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine (600 mg, 1.70 mmol) in THF (5 mL) and continue stirring for 2 h. Rapidly transfer the above solution via cannula to a solution of ethyl iodide (13.2 g, 84.9 mmol) in THF (5 mL) and continue stirring for 1 h. Quench with aqueous saturated ammonium chloride solution, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give

(±)-3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyanopropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a pale oil (350 mg, 68%). Use a method similar to the General Procedure 1-4 to give the title compound as an off-white solid. MS (ES+) *m/z*: 281 $(M+H)^+$.

Example 486

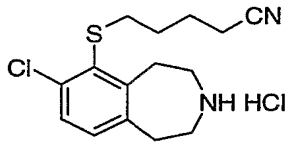
7-chloro-6-(1-cyano-1-methylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-cyanomethylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine (300 mg, 0.85 mmol) in THF (5 mL) at 0°C, add potassium *tert*-butoxide (480 mg, 4.26 mmol) at ambient temperature. After 15 min, add methyl iodide (3.02 g, 21.31 mmol) and continue stirring overnight at ambient temperature. Concentrate *in vacuo* and purify by chromatography on silica gel eluting with hexane/EtOAc (9:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(1-cyano-1-methyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (177 mg, 55%). MS (ES+) *m/z*: 282 $(M+H\text{-Boc})^+$. Use a method similar to the General Procedure 1-4 to give the title compound as an off-white solid. MS (ES+) *m/z*: 282 $(M+H)^+$.

Example 487

7-Chloro-6-(4-cyanobutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

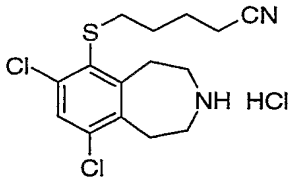


Use a method similar to the Example 387 to react 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 5-bromovaleronitrile. Purify by preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to

the General Procedure 2-2 to give the title compound as an off-white solid. MS (APCI+) *m/z*: 295 $(M+H)^+$.

Example 488

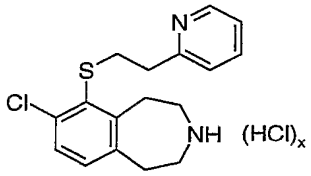
7,9-Dichloro-6-(4-cyanobutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Obtain the free base of the title compound as a minor product from Example 487, after preparative reverse phase HPLC (Column: Xterra Prep RP18 19x250mm; Solvent A: 10 mM aqueous ammonium carbonate, Solvent B: acetonitrile; 30-100% B over 20 minutes; flow rate 25 mL/min). Use a method similar to the General Procedure 2-2 to obtain the title compound as a tan solid. MS (ES+) *m/z*: 329 $(M+H)^+$.

Example 489

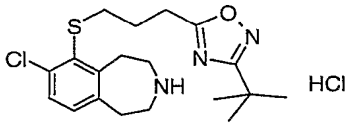
7-Chloro-6-(2-pyridin-2-yl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-(2-bromoethyl)-pyridine hydrobromide to give, after deprotection using a method similar to the General Procedure 1-4, the title compound. MS (ES+) *m/z* 319 $(M+H)^+$.

Example 490

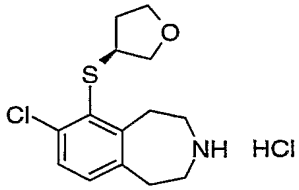
6-[3-(3-*tert*-Butyl-[1,2,4]oxadiazol-5-yl)-propylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 387, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 5-(3-bromopropyl)-3-*tert*-butyl-[1,2,4]oxadiazole to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z* 380 $(M+H)^+$.

Example 491

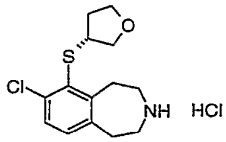
(-)-7-Chloro-6-(tetrahydrofuran-3-ylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 332, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (*S*)-toluene-4-sulfonic acid tetrahydrofuran-3-yl ester to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 284 $(M+H)^+$; $[\alpha]^{20}_D$ -28.0° (c 0.5, CH_3OH). ee = 97.8% [Chiral HPLC: Column: YMC ODS-AQ 120Å 4.6x50 mm [S-3μm]; eluent: gradient from 95:5 to 5:95 A/B; solvent A: water, 0.01% HFBA, 1% isopropanol; solvent B: acetonitrile, 0.01% HFBA, 1% isopropanol; flow rate 2 mL/min].

Example 492

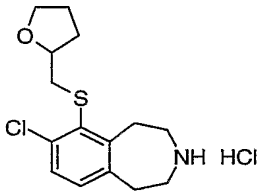
(+)-7-Chloro-6-(tetrahydrofuran-3-ylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 332, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and (*R*)-toluene-4-sulfonic acid tetrahydro-furan-3-yl ester to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (APCI+) *m/z*: 284 (M+H); $[\alpha]^{20}_{D}$ +32.5° (c 0.5, CH_3OH); ee = 95.7% [Chiral HPLC: Column: YMC ODS-AQ 120Å 4.6x50 mm [S-3μm]; eluent: gradient from 95:5 to 5:95 A/B; solvent A: water, 0.01% HFBA, 1% isopropanol; solvent B: acetonitrile, 0.01% HFBA, 1% isopropanol; flow rate 2 mL/min].

Example 493

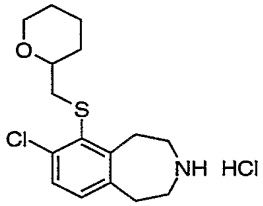
(±)-7-Chloro-6-(tetrahydrofuran-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-(bromomethyl)tetrahydrofuran to give, after deprotection by the General Procedure 1-4, the title compound as white crystals. MS (APCI+) *m/z*: 298 $(M+H)^+$.

Example 494

(±)-7-Chloro-6-(tetrahydropyran-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

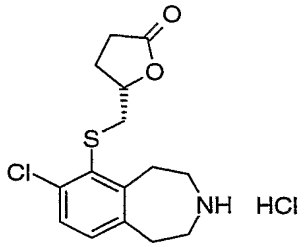


Use a method similar to the Example 330, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 2-

(bromomethyl)tetrahydropyran to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (APCI+) *m/z*: 312 $(M+H)^+$.

Example 495

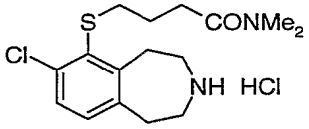
(S)-(+)-7-Chloro-6-(5-oxo-tetrahydrofuran-2-ylmethylthio)-2,3,4,5-tetrahydro-1H-benzo[d]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using (*S*)-3-*tert*-butoxycarbonyl-7-chloro-6-(5-oxo-tetrahydrofuran-2-ylmethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 312 $(M+H)^+$. $[\alpha]^{20}_D$ +78° (c 0.5, CH_3OH).

Example 496

7-Chloro-6-(3-dimethylcarbamoylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



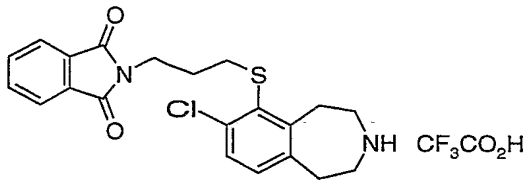
Treat a solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (385 mg, 0.90 mmol) in dioxane/water (1:1, 3.5 mL) with lithium hydroxide (43.0 mg, 1.01 mmol) at 80 °C for 1.5 h. Cool to ambient temperature, add aqueous saturated ammonium chloride and brine, extract three times with ethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Dissolve the residue in DCM (3.5 mL) and add EDC (162 mg, 0.84 mmol), 1-hydroxybenzotriazole (91.0 mg, 0.67 mmol), triethylamine (0.20 mL, 1.35 mmol), and dimethylamine (0.700 mL, 1.35 mmol). Stir overnight at ambient temperature. Dilute with water, extract with ethyl ether, dry over anhydrous $MgSO_4$, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc/methanol

60:40:1 to give 3-*tert*-butoxycarbonyl-7-chloro-6-(3-dimethylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine.

Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-(3-dimethylcarbamoyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine in DCM (1 mL) at ambient temperature and add 4M hydrogen chloride in dioxane (200 μL, 0.8 mmol). Continue stirring until TLC shows consumption of starting material. Concentrate *in vacuo*, triturate the obtained solid with dry diethyl ether and dry at 50° C under high vacuum overnight to give the title compound as a hygroscopic white solid (45.0 mg, 57%). MS (ES+) *m/z*: 327 $(M+H)^+$.

Example 497

7-Chloro-6-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

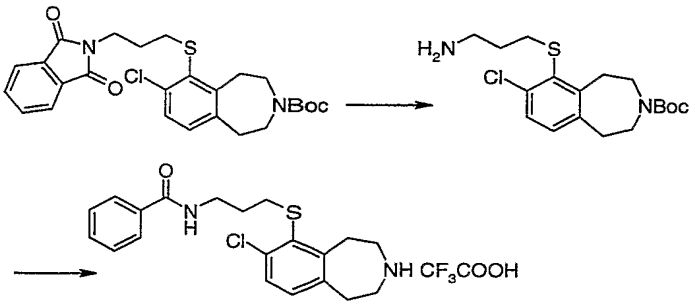


Dissolve 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (2.0 g, 5.20 mmol) in methanol (58 mL) and add potassium hydroxide (9.36 g, 167 mmol). Heat at 50 °C for 2 h. Cool to ambient temperature, add aqueous saturated ammonium chloride and water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo* to give 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.62 g, 5.20 mmol). Dissolve the crude 3-*tert*-butoxycarbonyl-7-chloro-6-mercapto-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.40 g, 4.46 mmol) in dry DMF (49.8 mL) and add DBU (0.80 mL, 5.35 mmol) and 3-bromopropyl phthalimide (1.55 g, 5.80 mmol). Stir at ambient temperature for 3 h. Add aqueous saturated ammonium chloride and water. Extract twice with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (6:1) to give the free base of title compound (1.64 g, 74%).

Use a method similar to the General Procedure 1-5, to deprotect 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and purify by preparative reverse phase HPLC to give the title compound. MS (APCI+) *m/z* 401 $(M+H)^+$.

Example 498

6-(3-Benzoylaminopropylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

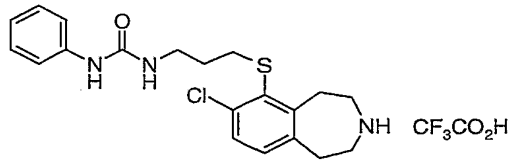


Suspend 3-*tert*-butoxycarbonyl-7-chloro-6-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.20 g, 2.39 mmol) in ethanol (53.2 mL), add hydrazine (0.150 mL, 4.78 mmol) and heat at 65 °C for 2 h. Cool to ambient temperature, filter from precipitate, and concentrate *in vacuo* to provide the 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (861 mg, 97%). MS (APCI+) *m/z*: 371 $(M+H)^+$.

To a solution of 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (46.7 mg, 0.126 mmol) in dry DCM (0.5 mL) at ambient temperature under nitrogen, add triethylamine (19.3 μL, 0.139 mmol) and benzoyl chloride (16.1 μL, 0.139 mmol). Stir at ambient temperature for 2.5 h. Add aqueous saturated ammonium chloride and water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Dissolve the residue in DCM (0.16 mL), add trifluoroacetic acid (44.6 μL, 0.58 mmol) and stir for 18 h at ambient temperature. Concentrate *in vacuo* and purify by preparative HPLC [Column: YMC ODS-AQ 120Å 20x250mm [S10-20μm]; eluent: 95:5 to 5:95 A/B; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol; flow rate 20 mL/min] to give the title compound (7.0 mg, 12%). MS (APCI+) *m/z* 375 $(M+H)^+$.

Example 499

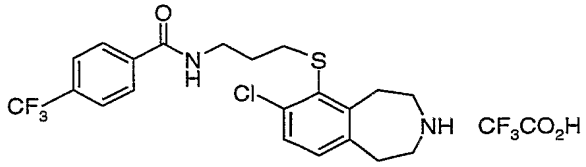
6-[3-(3-Phenylureido)-propylthio]-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 498, using phenyl isocyanate, to give the title compound. MS (APCI+) *m/z* 390 $(M+H)^+$.

Example 500

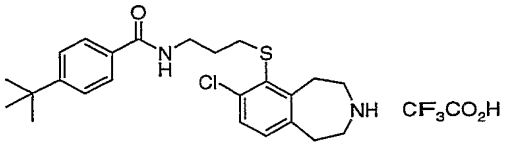
7-Chloro-6-[3-(4-trifluoromethylbenzoylamino)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



To a stirred solution of 4-trifluoromethylbenzoic acid (60.0 mg, 0.316 mmol) in anhydrous DMF (1.2 mL) at ambient temperature under nitrogen, add EDC (63.6 mg, 0.332 mmol), 1-hydroxybenzotriazole (44.8 mg, 0.332 mmol), 4-dimethylaminopyridine (40.5 mg, 0.332 mmol) and a solution of 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (123 mg, 0.332 mmol) in DCM (2 mL). Stir for 18 h at ambient temperature. Add water, extract twice with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Treat the residue with trifluoroacetic acid (0.272 mL, 0.640 mmol) in DCM (0.451 mL) at ambient temperature for 18 h. Concentrate *in vacuo* and purify by preparative reverse phase HPLC [Column: YMC ODS-AQ 120Å 20x250mm [S10-20μm]; eluent: 95:5 to 5:95 A/B; solvent A: water, 0.1% TFA, 1% isopropanol; solvent B: acetonitrile, 0.05% TFA, 1% isopropanol; flow rate 20 mL/min] to give the title compound as a white solid (31.0 mg, 18%). MS (APCI+) *m/z* 443 $(M+H)^+$.

Example 501

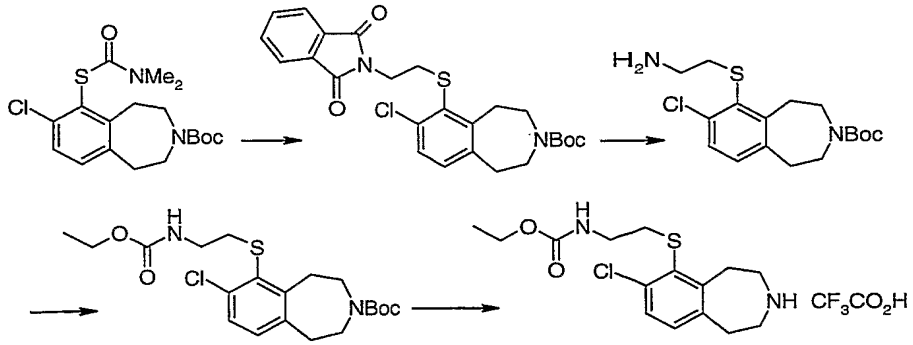
7-Chloro-6-[3-(4-*tert*-butylbenzoylamino)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 500, using 6-(3-aminopropylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and 4-*tert*-butyl benzoic acid to give the title compound as a white solid. MS (APCI+) *m/z* 431 $(M+H)^+$.

Example 502

7-Chloro-6-(2-ethoxycarbonylamino-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

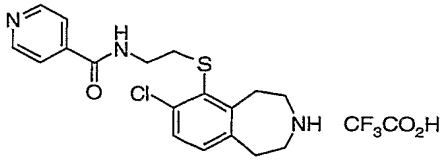


Use a method similar to the Example 497, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*- benzo[*d*]azepine and 3-bromoethyl phthalimide to give 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. MS (ES+) *m/z* 357 $(M+H)^+$.

Use a method similar to the Example 498, using 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and ethyl chloroformate to give, after deprotection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (APCI+) *m/z*: 329 $(M+H)^+$.

Example 503

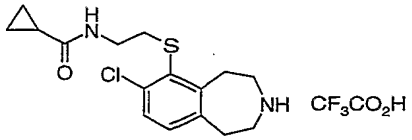
7-Chloro-6-{2-[(pyridine-4-carbonyl)amino]-ethylthio}-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 500, using 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and isonicotinic acid to give the title compound. MS (ES+) *m/z*: 362 $(M+H)^+$.

Example 504

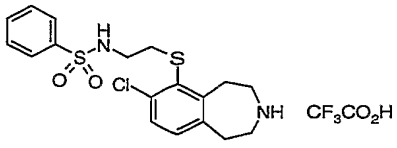
7-Chloro-6-[2-(cyclopropanecarbonylamino)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 498, using 6-(3-aminoethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and cyclopropanecarbonyl chloride to give, after deprotection using a method similar to the General Procedure 1-5, the title compound. MS (ES+) *m/z*: 325 $(M+H)^+$.

Example 505

6-(2-Benzenesulfonylamino-ethylthio)-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate

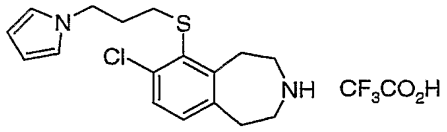


Use a method similar to the Example 498, using 6-(3-amino-ethylthio)-3-*tert*-butoxycarbonyl-7-chloro-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and benzenesulfonyl

chloride to give, after de protection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (APCI+) *m/z*: 397 $(M+H)^+$.

Example 506

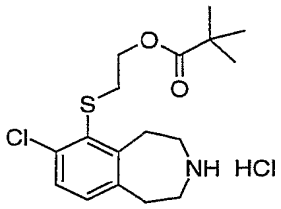
7-Chloro-6-(3-pyrrol-1-yl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Trifluoroacetate



Use a method similar to the Example 497, using 3-*tert*-butoxycarbonyl-7-chloro-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and *N*-(3-bromopropyl)pyrrole to give, after deprotection using a method similar to the General Procedure 1-5, the title compound as a white solid. MS (ES+) *m/z*: 321 $(M+H)^+$.

Example 507

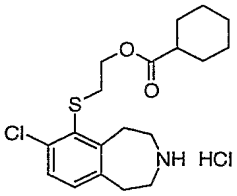
7-Chloro-6-[2-(2,2-dimethylpropionyloxy)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxyethylthio)-2,3,4,5-tetrahydrobenzo[d]azepine (85 mg, 0.238 mmol) in DCM (3 ml) at 0°C, add triethylamine (331 µl, 2.381 mmol) followed by trimethylacetyl chloride (147 µl, 1.190 mmol). Continue stirring for 15 min, dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Deprotection by the General Procedure 1-5, basic workup, and by the General Procedure 2-2 give the title compound. MS (ES+) *m/z* 342 (M+H).

Example 508

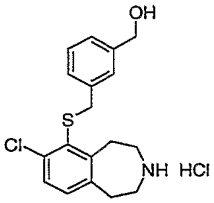
7-Chloro-6-(2-cyclohexanecarbonyloxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 507, using cyclohexanecarbonyl chloride, to give the title compound. MS (ES+) *m/z* 368 (M+H).

Example 509

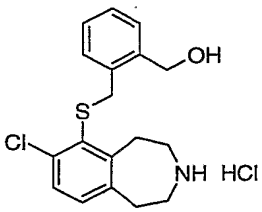
7-Chloro-6-(3-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 242, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 510

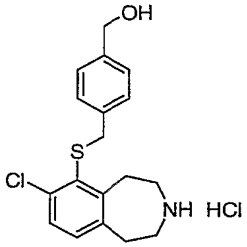
7-Chloro-6-(2-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 242, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection by the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 511

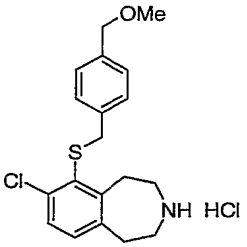
7-Chloro-6-(4-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z*: 334 $(M+H)^+$.

Example 512

7-Chloro-6-(4-methoxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

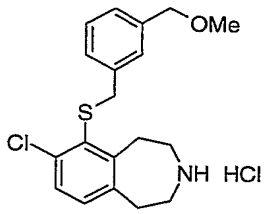


To a stirred solution of 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (133 mg, 0.306 mmol) in anhydrous DMF (2 mL) under nitrogen, add sodium hydride (60% dispersion, 13-15 mg, 0.375 mmol) at ambient temperature and continue stirring for 30 min. Add methyl iodide (80 □L, 1.28 mmol). After 15 min, dilute with water, extract three times with EtOAc, dry over anhydrous $MgSO_4$ and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (15:1) to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-

methoxymethyl-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a clear oil, which crystallizes on standing to a white solid (87 mg, 63%), along with recovered starting material (22 mg, 17%). Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z*: 348 $(M+H\text{-}Boc)^+$.

Example 513

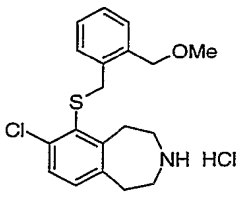
7-Chloro-6-(3-methoxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 348 (M+H).

Example 514

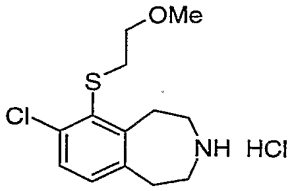
7-Chloro-6-(2-methoxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxymethylbenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 348 (M+H).

Example 515

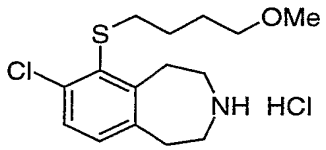
7-Chloro-6-(2-methoxyethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride



Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxy-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z*: 272 (M+H).

Example 516

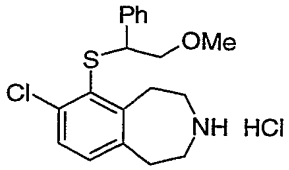
7-Chloro-6-(4-methoxybutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride



Use a method similar to the Example 478, using 3-*tert*-butoxycarbonyl-7-chloro-6-(3-methoxycarbonyl-propylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxybutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine. Use a method similar to the Example 512, using 3-*tert*-butoxycarbonyl-7-chloro-6-(4-hydroxybutylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give the title compound as a white solid. MS (ES+) *m/z*: 300 $(M+H)^+$.

Example 517

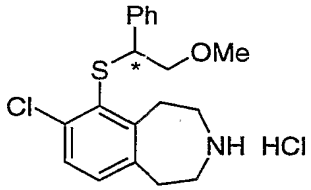
(±)-7-Chloro-6-(2-methoxy-1-phenylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 512, using (±)-3-*tert*-butoxycarbonyl-7-chloro-6-(2-hydroxy-1-phenylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection by a method similar to the General Procedure 1-4, the title compound as an off-white solid. MS (ES+) *m/z*: 348 $(M+H)^+$.

Example 518

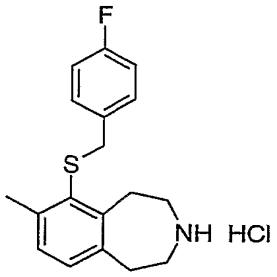
(-)-7-Chloro-6-(2-methoxy-1-phenylethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Separate the enantiomers of (±)-7-chloro-6-(2-methoxy-1-phenyl-ethylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral normal phase chromatography (Chiralcel OJ 8x33 cm column, eluting with 0.2% DMEA in ethanol/heptane, 40:60). Collect the second eluting isomer and use the General Procedure 2-2 to give the title compound as a white solid (76 mg, 29%). MS (ES+) *m/z*: 349 $(M+H)^+$. $[\alpha]^{20}_D$ -176° (c 0.5, CH_3OH).

Example 519

6-(4-Fluorobenzylthio)-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride

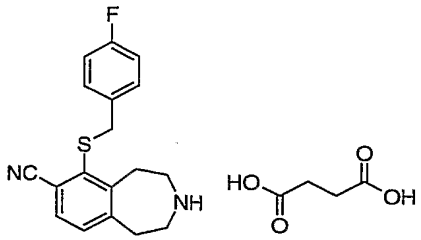


Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (75 mg, 0.206 mmol) and 4-fluorobenzyl bromide (195 mg, 1.03 mmol) to give, after chromatography on silica gel eluting with hexane/EtOAc (1:0, 9:1 and 4:1), 3-*tert*-butoxycarbonyl-6-(4-fluorobenzylthio)-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as an oil (59 mg, 71%). MS (ES+) *m/z*: 302 $(M+H\text{-}Boc)^+$.

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-6-(4-fluoro-benzylthio)-7-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (55 mg, 0.137 mmol) to give the title compound as a white solid (42 mg, 91%). MS (ES+) *m/z*: 285 $(M+H)^+$.

Example 520

7-Cyano-6-(4-fluorobenzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate



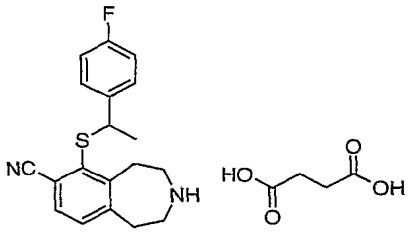
Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-cyano-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (123 mg, 0.33 mmol) and 4-fluorobenzyl bromide (204 mg, 1.64 mmol), to give 3-*tert*-butoxycarbonyl-7-cyano-6-(4-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (118 mg, 87%).

Use a method similar to the General Procedure 1-4, using 3-*tert*-butoxycarbonyl-7-cyano-6-(4-fluoro-benzylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (118 mg, 0.286

mmol) to give, after basic work-up, the free base of the title compound (89 mg, 100%). MS (ES+) *m/z* 313 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound (123 mg, 100%). MS (ES+) *m/z* 313 $(M+H)^+$.

Example 521

(±)-7-Cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate

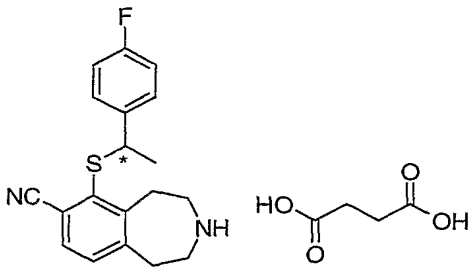


Use a method similar to the General Procedure 7, using 3-*tert*-butoxycarbonyl-7-cyano-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (171 mg, 0.46 mmol) and (±)-1-(4-fluorophenyl)ethyl bromide (377 mg, 1.85 mmol) to give, after purification by chromatography on silica gel, (±)-3-*tert*-butoxycarbonyl-7-cyano-6-[1-(4-fluorophenyl)-ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine as a colorless oil (10.3 mg, 5.3%). MS (ES+) *m/z* 449 $(M+Na)^+$, 465 $(M+K)^+$.

Use a method similar to the General Procedure 1-5, using (±)-3-*tert*-butoxycarbonyl-7-cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (10.3 mg, 0.024 mmol) to give, after basic work-up, the free base of the title compound (6.8 mg, 87%). MS (ES+) *m/z* 327 $(M+H)^+$. Use a method similar to the General Procedure 2-1 to give the title compound as a white solid (9.3 mg, 87%). MS (ES+) *m/z* 327 $(M+H)^+$.

Example 522

7-Cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Succinate, Isomer 1

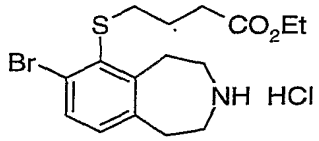


Separate the two enantiomers of (±)-7-cyano-6-[1-(4-fluorophenyl)ethylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine by chiral HPLC (Chiralpak AD-H 15cm x 4.6mm column with a 5 μm packing size. Elute with heptane/ethanol (95:5) containing 0.2% DEA at 0.5 mL/min with an injection volume of 10.00 μL).

Subject the first eluting isomer (t_R = 17.2 min, ee > 99%) to the General Procedure 2-1 to afford the title compound as a white solid. MS (ES+) *m/z* 327 $(M+H)^+$.

Example 523

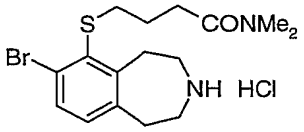
7-Bromo-6-(3-ethoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-7-bromo-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and ethyl 4-bromobutyrate to give, after deprotection by a method similar to the General Procedure 1-4, the title compound. MS (ES+) *m/z*: 374 $(M+H)^+$.

Example 524

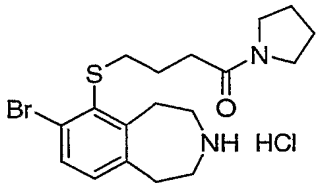
7-Bromo-6-(3-dimethylcarbamoylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 523, using 7-bromo-3-*tert*-butoxycarbonyl-6-(3-ethoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine, to give the title compound as a white solid. MS (ES+) *m/z*: 373 $(M+H)^+$.

Example 525

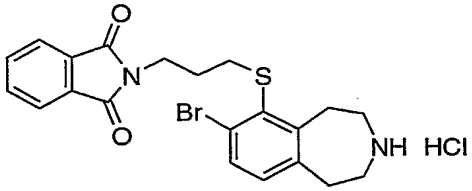
7-Bromo-6-(4-oxo-4-pyrrolidin-1-yl-butylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 523, using 7-bromo-3-*tert*-butoxycarbonyl-6-(3-ethoxycarbonylpropylthio)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine and pyrrolidine to give the title compound. MS (ES+) *m/z*: 397 $(M+H)^+$.

Example 526

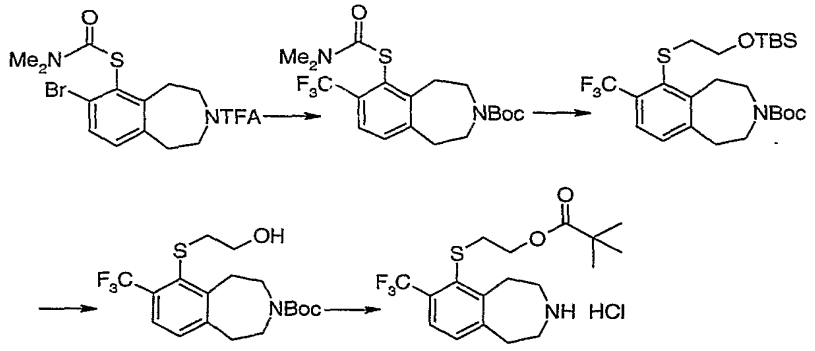
7-Bromo-6-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propylthio]-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



Use a method similar to the Example 497 to react 7-bromo-3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine with 3-bromopropyl phthalimide. Use a method similar to the General Procedure 1-4 to give the title compound as a white solid. MS (ES+) *m/z* 445 $(M+H)^+$.

Example 527

6-[2-(2,2-Dimethylpropionyloxy)-ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine Hydrochloride



3-*tert*-Butoxycarbonyl-6-dimethylcarbamoylthio-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[*d*]azepine: To a stirred solution of 7-bromo-6-dimethylcarbamoylthio-3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (1.383 g, 3.254 mmol), in NMP (40 ml) add sodium trifluoromethyl acetate (3.54 g, 26.03 mmol), copper(I) iodide (2.47 g, 13.0 mmol) and heat the mixture at 180 °C for 4 h. Cool to ambient temperature. Dilute with EtOAc, water and remove the copper solid residue by filtration. Separate the layers of filtrate and extract the aqueous layer three times with EtOAc. Dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (6:1) to give the desired intermediate as a yellow oil (882 mg, 74%).

3-*tert*-Butoxycarbonyl-6-[2-(*tert*-butyl-dimethylsilanyloxy)ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the Preparation 177, using 3-*tert*-butoxycarbonyl-6-dimethylcarbamoylthio-7-trifluoromethyl-2,3,4,5-tetrahydro-benzo[*d*]azepine and (2-bromoethoxy)-*tert*-butyldimethylsilane to give the desired intermediate.

3-*tert*-Butoxycarbonyl-6-(2-hydroxyethylthio)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Dissolve 6-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H* -benzo[*d*]azepine (153 mg, 0.303 mmol) in THF (3 mL). Add 1.0 M tetrabutylammonium fluoride in THF (600 µL, 0.606 mmol,) and stir

overnight. Dilute with water, extract three times with EtOAc, dry over anhydrous Na_2SO_4, and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with hexane/EtOAc (85:15) to give the desired intermediate.

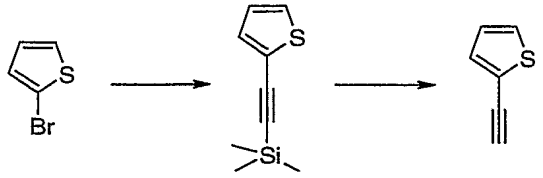
6-[2-(2,2-Dimethylpropionyloxy)-ethylthio]-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine hydrochloride: Use a method similar to the Example 507, using 3-*tert*-butoxycarbonyl-6-(2-hydroxyethylthio)-7-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine to give, after deprotection using a method similar to the General Procedure 1-4, the title compound as a white solid. MS (ES+) *m/z*: 376 $(M+H)^+$.

General Procedure 8

Dissolve the appropriate bromide (2 equiv.) in isopropylamine (300-400 equiv.) at room temperature, under nitrogen, then add palladium(II) bis(benzonitrile) dichloride (0.2 equiv.), triphenylphoshine (0.4 equiv.) and copper(I) iodide (0.2 equiv.). Degas the solution and purge with nitrogen, then add the appropriate alkyne (1.0 equiv.). Seal the reaction vessel, stir at room temperature for 30 min, then at 75 °C for 3-4 h. Remove most of the solvent *in vacuo*, add diethyl ether and 2M aqueous HCl. Dry the organic layer over $MgSO_4$, filter and concentrate *in vacuo*. Purify by chromatography on silica gel eluting with isohexane/EtOAc or hexane/EtOAc mixtures.

Preparation 249

2-Ethynyl-thiophene

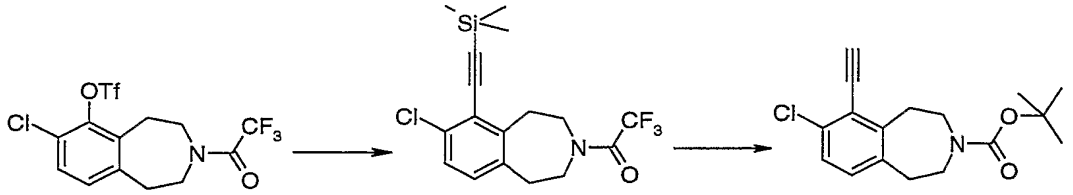


Trimethyl-thiophen-2-ylethynyl-silane: Use a method similar to the General Procedure 8 to couple 2-bromo-thiophene (0.97 mL, 10 mmol) with ethynyl-trimethylsilane (2.82 mL, 20 mmol). Purify by chromatography on silica gel eluting with isohexane to give the desired intermediate (1.46 g, 81%). GC-MS *m/z* 180 (M^+).

2-Ethynyl-thiophene: Add a saturated solution of potassium carbonate in methanol (7.5 mL) to trimethyl-thiophen-2-ylethynyl-silane (540 mg, 3 mmol) in deoxygenated methanol (100 mL) at room temperature under nitrogen. Stir the reaction for 3.5 h, then dilute with dichloromethane (100 mL) and wash with water (3 x 100 mL). Remove the organic layer, dry using an ISCO® phase separator and then concentrate *in vacuo* to give the title compound (302 mg, 93%).

Preparation 250

3-*tert*-Butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine



7-Chloro-3-(2,2,2-trifluoroacetyl)-6-trimethylsilanylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Use a method similar to the General Procedure 3 to couple 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trifluoromethanesulfonyloxy-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (425 mg, 1 mmol) with 2-trimethylsilylacetylene (0.28 mL, 2 mmol). Purify by chromatography on silica gel eluting with isohexane/EtOAc (100:0 to 85:15 gradient over 40 min) to give the desired intermediate (247 mg, 81%). MS (ES+) *m/z*: 306 $(M+H)^+$.

3-*tert*-Butoxycarbonyl-7-chloro-6-ethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine: Add a solution of potassium carbonate (999 mg, 7.2 mmol) in water (5 mL) to 7-chloro-3-(2,2,2-trifluoroacetyl)-6-trimethylsilanylethynyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (180 mg, 0.48 mmol) in methanol (10 mL) and stir at room temperature, under nitrogen for 1.5 h. Add di-*tert*-butyl-dicarbonate (115 mg, 0.53 mmol) in dichloromethane (8 mL) and stir for 3 days. Add another solution of di-*tert*-butyl-dicarbonate (115 mg, 0.53 mmol) in dichloromethane (5 mL) and stir for 2 h. Add water (10 mL) and dichloromethane (10 mL) and separate the organic layer. Extract the aqueous layer with dichloromethane (3 x 10 mL) and combine the organic layers. Dry using an ISCO® phase separator and concentrate. Purify by chromatography on silica gel eluting with